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Lacking in substantial evidence of effectiveness as a fixed combination: For relief from coughing, upper respiratory congestion and hypersecretion associated with the common cold, sinusitis, vasomotor rhinitis and allergic rhinitis.

Final classification of the less-than-effective indications requires further investigation.

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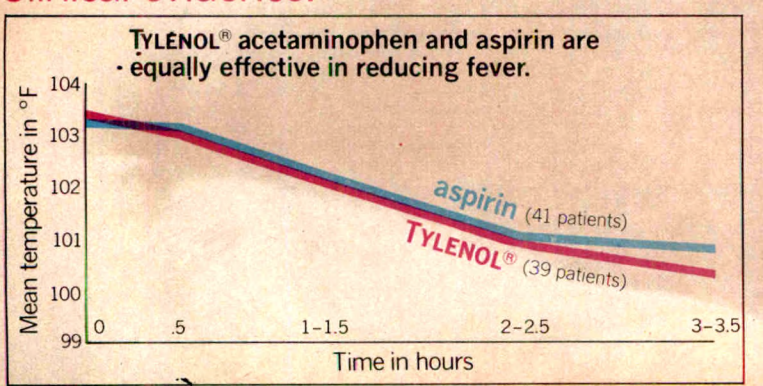

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Final classification of the less-than-effective indications requires further investigation.

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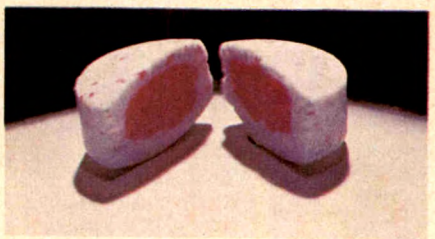

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Phenylephrine hydrochloride	5.0 mg.	5.0 mg.	10.0 mg.
Phenyltoloxamine citrate	7.5 mg.	7.5 mg.	15.0 mg.
Chlorpheniramine maleate	2.5 mg.	2.5 mg.	5.0 mg.

Each teaspoonful (5 ml.) of syrup contains:

Phenylpropanolamine hydrochloride	20.0 mg.
Phenylephrine hydrochloride	5.0 mg.
Phenyltoloxamine citrate	7.5 mg.
Chlorpheniramine maleate	2.5 mg.

Each pediatric formulation contains the following ingredients:	Pediatric Syrup each 5 ml. contains:	Pediatric Drops each 1-ml. dropper contains:
Phenylpropanolamine hydrochloride	5.0 mg.	5.0 mg.
Phenylephrine hydrochloride	1.25 mg.	1.25 mg.
Phenyltoloxamine citrate	2.0 mg.	2.0 mg.
Chlorpheniramine maleate	0.5 mg.	0.5 mg.

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Rhinorrhea	Lacrimation
Postnasal drip	Sneezing
Nasal congestion	Itching of eyes and nose
Sinus congestion	Head stuffiness

CONTRAINDICATIONS: Sensitivity to any of the ingredients.

PRECAUTIONS: This preparation may cause drowsiness. The patient should be cautioned against engaging in operations requiring alertness such as driving an automobile, operating machinery, etc. Do not exceed the recommended dose unless directed by a physician. Individuals with high blood pressure, heart disease, diabetes mellitus, thyroid disease, glaucoma, peripheral vascular disease or prostatic hypertrophy should use only as directed by a physician.

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6 to 12 months	1/2 ml.	1/2 teaspoonful		
1 to 6 years	1 ml.	1 teaspoonful		
6 to 12 years		2 teaspoonfuls	1/2 teaspoonful	1/2 tablet
over 12 years			1 teaspoonful	1 tablet

REFERENCES:

1. New and Nonofficial Remedies 1955.
2. New and Nonofficial Remedies 1954.
3. A.M.A. Council on Drugs Monograph on Phenyltoloxamine, J.A.M.A. 163:357 (2/2/57).
4. New and Nonofficial Drugs 1959.

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Titles.—Titles should be short, specific, and clear. They should not exceed 42 characters per line, including punctuation and spaces, and be limited to two lines. The title page should include the full names and academic affiliations of all authors, the address to which requests for reprints should be sent, and, if the manuscript was presented at a meeting, the name of the organization, place, and date on which it was read.

Abstract.—Provide an abstract (135-word maximum) of the article, including statement of the problem, method of study, results, and conclusions. The abstract replaces the summary.

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1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 131:295-296, 1977.
2. Koller LR: *Ultraviolet Radiation*, ed 2. New York, John Wiley & Sons Inc, 1965, pp 141-160.
3. Daughaday WH: The adenohypophysis, in Williams RH (ed): *Textbook of Endocrinology*, ed 5. Philadelphia, WB Saunders Co, 1974, pp 31-79.

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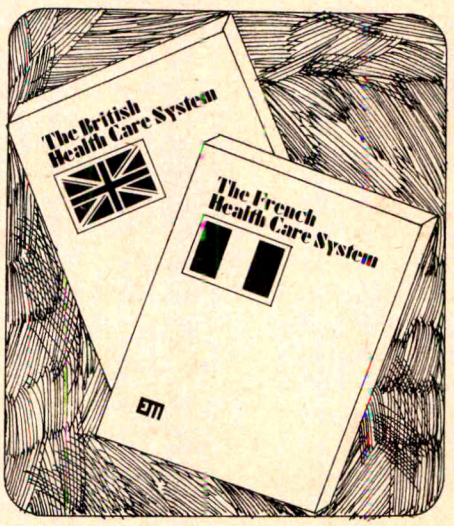

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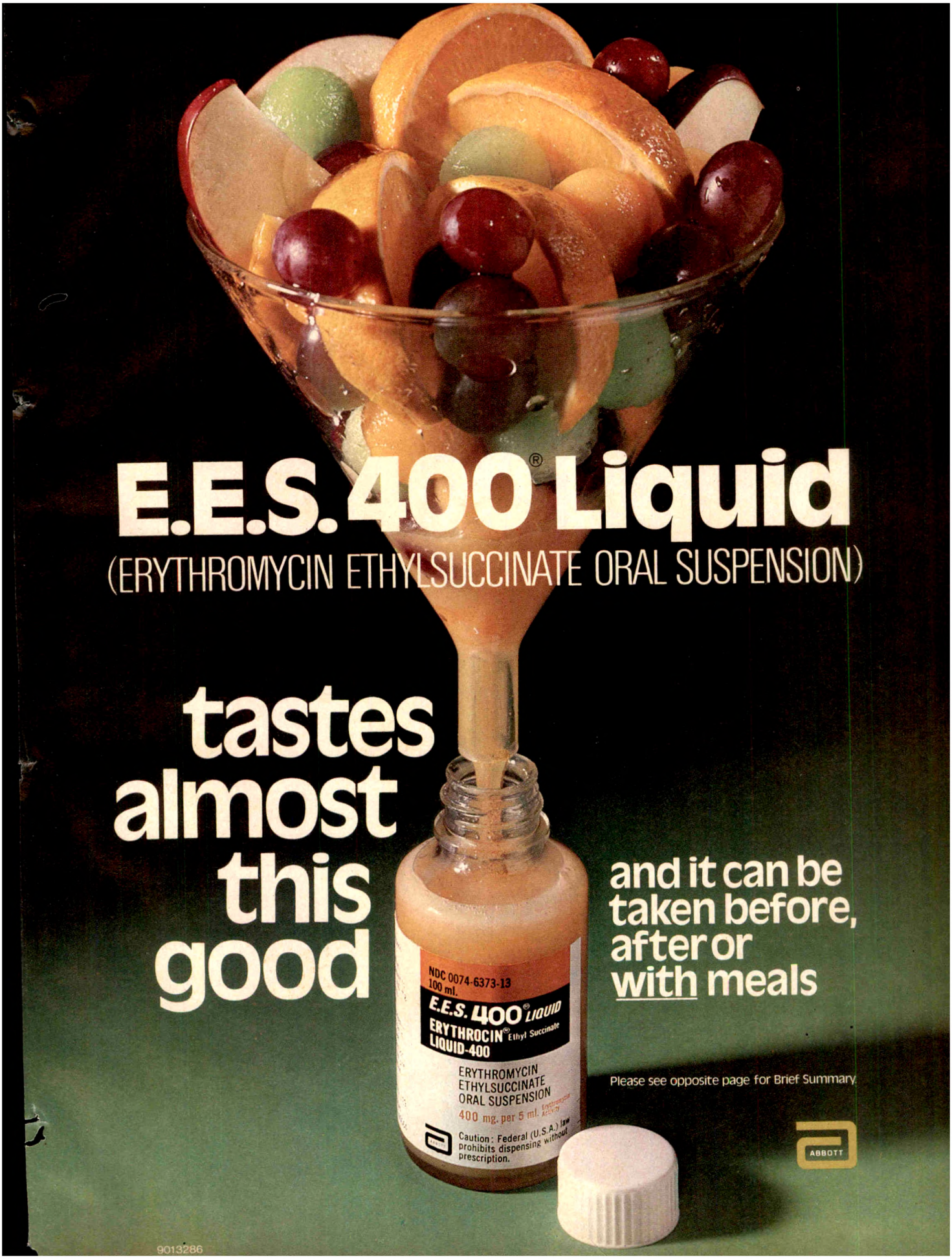
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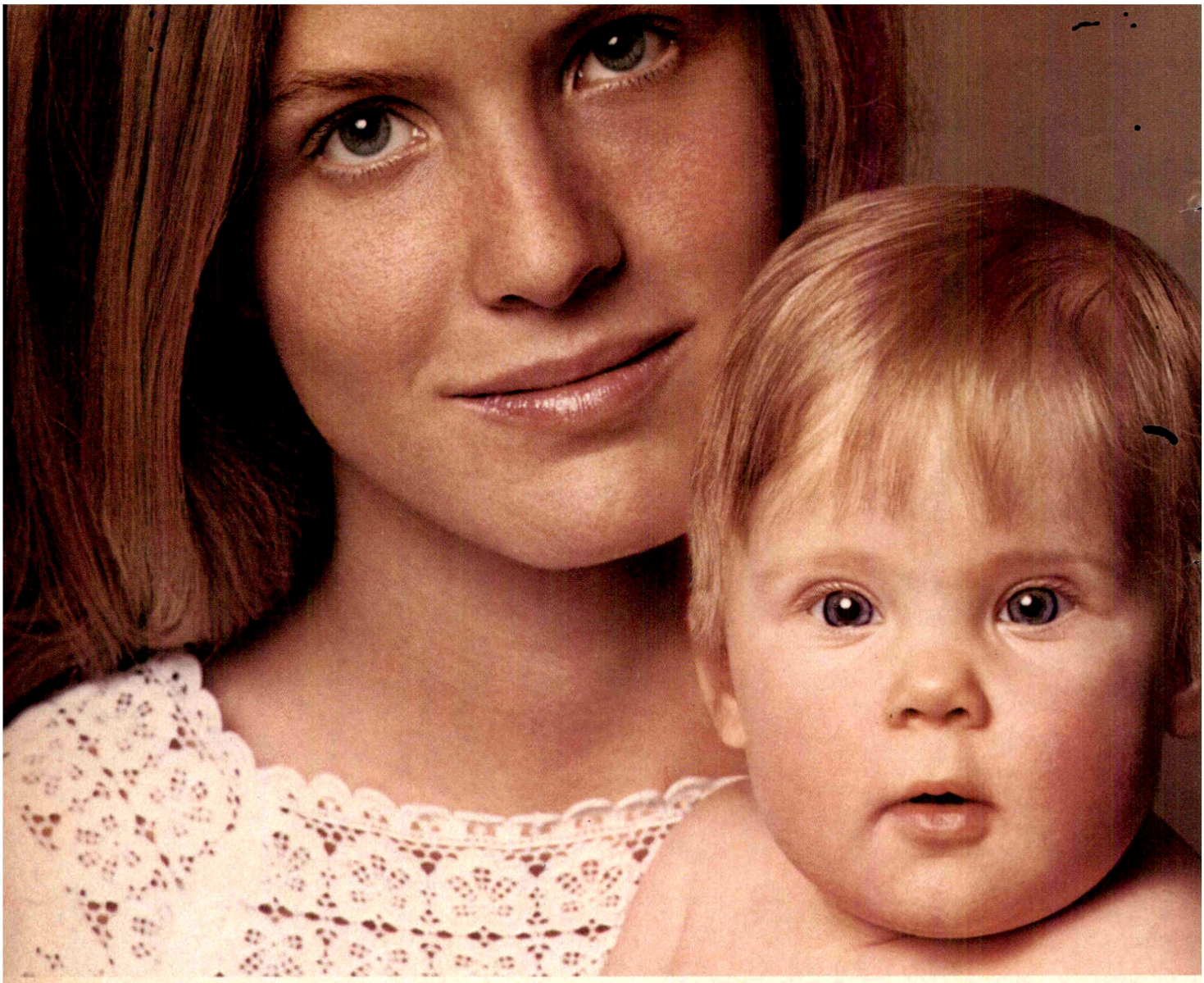

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[1] Material presented at March 23, 1977, symposium, Infant Nutrition: A Foundation for Lasting Health?

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Progress and the Little Gray Pill

The superiority of synthetic levothyroxine sodium over thyroid extracts in the treatment of hypothyroidism seems established. The exciting developments in our understanding of thyroid physiology during recent years must parallel the excitement that accompanied the first demonstration of the effective control of hypothyroidism by the use of extracts from animal thyroid glands. Those of us who have witnessed some of these advances remember the excitement that they produced, and we have enjoyed and appreciated the advantages that they have provided. Progress is always rewarding, and I agree with Penny and Frasier (p 16) that synthetic levothyroxine is the drug of choice in the treatment of hypothyroidism in the year 1979. However, I am compelled to add a word in defense of an old and reliable friend, namely, the little gray pill of USP desiccated thyroid. To do less would seem unjust.

For many years, I have prescribed levothyroxine for my new patients with hypothyroidism, and I agree that it offers several advantages, most all of which represent convenience rather than demonstrated clinical importance. The many thousands of patients successfully treated with USP thyroid preparations attest to their value.

In treating patients who have hypothyroidism, every physician knows or should know that the response to thyroid hormone varies no matter in what form the drug is administered, and reports of triiodothyronine-induced hyperthyroidism in an occasional patient treated with USP thyroid preparations should be no surprise. More surprising, of greater interest, and perhaps of greater importance, is the fact that the patients described by Penny and Frasier did not have clinical evidence of hyperthyroidism, even after receiving USP thyroid for years, during which time they (at least intermittently) had elevated levels of circulating triiodothyronine in the presence of normal levels of thyroxine.

If the chemical findings in the patients described accurately reflect chemical changes in all patients treated with USP thyroid, a generation of persons has grown up with hypertriiodothyronemia. If these many thousands of persons have suffered ill effects from such a chemical abnormality, they have not come to our attention; indeed, the evidence is to the contrary.

At the present time, approximately 40% of all patients in the United States receiving thyroid hormone therapy are taking USP thyroid. Many of them justifiably resist changing to a new preparation after enjoying years of satisfactory, even dramatic, response to the little gray pill. Further, many physicians with years of experience using USP thyroid have learned how to use these preparations and appreciate their effectiveness and reliability. They, too, will likely be more impressed by clinical success than the demonstration of a poorly understood chemical change in the blood.

Levothyroxine is rapidly replacing USP thyroid, and so it should; but USP thyroid, like levothyroxine, must be properly administered. When so administered, either preparation can be expected to control hypothyroidism satisfactorily. As we watch the passing of USP thyroid therapy, let us not be too critical of the little gray pill, for its record of success is long and enviable.

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Functioning Tumors

It was 1952 when Hawfield and Daisley[1] described in detail the clinical picture and the diagnostic evaluation of the condition of a 13-month-old girl with severe chronic diarrhea, whose abnormal stools ceased promptly after removal of a ganglioneuroma from the right adrenal gland. They wrote, "Laboratory efforts to identify an endocrine function of the tumor removed in this case failed to reveal any functional secretion. Despite this fact, the clinical improvement indicates beyond a doubt that the tumor did have an endocrine function and was responsible for the presenting signs and symptoms."

Seven years later, Dicke and coworkers[2] and Greenberg and Gardner[3] simultaneously reported evidence of increased catecholamine production in patients with ganglioneuroma and chronic diarrhea. Since the urinary excretion of the various compounds returned to normal after excision of the tumor, the catecholamines were believed to be important in the cause of the diarrhea, although the exact mechanism was not clear. Subsequent studies by numerous investigators confirmed that most neuroblastomas and ganglioneuroblastomas were hormone-producing tumors and could synthesize dopamine and norepinephrine. Measurement of these compounds and their metabolites became an important tumor marker, and an aid in diagnosis and follow-up care of patients. Although most children with these neoplasms excreted increased amounts of catecholamines, very few of them had chronic diarrhea. Furthermore, patients with pheochromocytomas who had a sharp elevation of norepinephrine and epinephrine output seldom had diarrhea. It seemed probable that humoral substance(s) other than catecholamines were responsible for the severe disturbance of gastrointestinal (GI) function in certain patients with neurogenic tumors.[4]

The mystery remained until 1973 when Bloom et al[5] found vasoactive intestinal peptide (VIP) in a retroperitoneal ganglioneuroblastoma of an adult with the watery diarrhea, hypokalemia, achlorhydria syndrome. Then Swift et al[6] reported VIP in a thoracic ganglioneuroma from a 5-year-old girl who had diarrhea, stridor, and abnormally high quantities of catecholamines and metabolites in her urine. The diarrhea ceased after partial removal of the tumor and a decrease in VIP levels, even though catecholamine output remained elevated. This evidence implicated the GI hormone VIP as the culprit in causing the diarrhea, and demonstrated that both VIP and catecholamines can be produced by neurogenic tumors. Other investigators subsequently described similar findings.

The vasoactive effects of VIP and norepinephrine are antagonistic; VIP is a potent vasodilator and norepinephrine is a potent vasoconstrictor. Thus, children with the ganglioneuroma-diarrhea syndrome potentially are at risk, particularly during surgical excision of their tumors. Hypotensive or hypertensive crises can develop depending on the predominant hormone released by the tumor. Although such events are uncommon in children, preoperative and intraoperative management, as described by Kaplan and his colleagues (p 21), provides optimum care to the patient whose ganglioneuroma secretes both VIP and norepinephrine.

It is not surprising that both peptide hormone and catecholamine production have been identified in sympathetic nervous system tumors. Ganglion cells belong to the amine precursor uptake and decarboxylation (APUD) series that produce more than 35 physiologically active peptides and a small number of active amines.[7] These cells are widely distributed throughout the body and constitute the diffuse neuroendocrine system, whose central division contains the neuroendocrine and endocrine cells of the hypothalamic-pituitary axis and pineal gland and whose peripheral division includes all the APUD cells outside this region. The majority of the peripheral cells are located in the GI tract and the pancreas, but APUD cells also are found in the thyroid, parathyroid, adrenal medulla, sympathetic nervous system, and other areas. These cells at one time were presumed to have a common origin from neural crest ectoderm. Now they are thought to be "neuroendocrine programmed," arising either in the embryonic epiblast or in one of its descendants.

Studies have shown that there is

structural similarity among many of the biologically active peptides, ie, glucagon and secretin have 14 amino acid identities. Some gut hormones, such as cholecystokinin, are common to both intestinal tract and brain, and may effect hypothalamic activity and be involved in control of appetite.[8] Contrariwise, central neuronal peptides have been found in endocrine cells of the intestine and pancreas, ie, somatostatin may play a role in relation to the GI portal system as well as in inhibiting growth hormone release.

It is clear that our perspective of endocrine cells and hormones has been broadened considerably by the recent explosive increase in new knowledge. Cells capable of producing peptides and amines are located throughout the body. Words such as "GI hormones" or "brain hormones" are too restrictive. Neoplasms arising from a variety of tissues can harbor populations of cells that are capable of secretory product production. Many of them are named according to their secretory product, ie, insulinoma, glucagonoma, somatostatinoma, VIPoma. Although the majority of these tumors have been described in adults to date, it is important that child-care physicians become familiar with the signs and symptoms caused by hypersecretion of the major peptide and amine hormones. Unexplained disorders involving diarrhea, hypoglycemia or hyperglycemia, flushing, hypertension, etc, may be caused by excessive production of these secretory products by tumors.

Of equal importance is an understanding of the multiple endocrine adenomatosis syndromes.[9] These are familial disorders characterized by the presence of hyperplasia or tumor that involves one or more endocrine gland concurrently. Pluriglandular disease may be masked for many years by a clinical picture that suggests single endocrine gland involvement, or signs and symptoms of multiple organ involvement can develop simultaneously. When one affected family member has been identified, others should be evaluated for an endocrinopathy.

Multiple endocrine adenomastosis I (Wermer's syndrome or multiple endocrine neoplasia type 1) is characterized by the concomitant occurrence of benign tumors of the anterior pituitary gland, hyperplasia of the parathyroid glands, benign or malignant tumors of the pancreatic islet cells, and peptic ulceration. Multiple endocrine adenomatosis II (Sipple's syndrome or multiple endocrine neoplasia type 2) includes medullary carcinoma of the thyroid, pheochromocytoma and parathyroid hyperplasia, or tumor. The major components of multiple endocrine adenomatosis III are neuroma, medullary thyroid carcinoma, and pheochromocytoma.

All of these syndromes have been described in children. Once one part of a syndrome is identified, a search should be made for the other components. The full-blown clinical picture may take years to develop. Hypersecretion of peptides, amines, or other substances by the neuroendocrine cells are primary markers for the disorders. Hypercalcemia suggests parathyroid dysfunction. Pheochromocytomas produce catecholamines. Increased calcitonin levels are found in medullary carcinoma of the thyroid. Pancreatic islet cell tumors release insulin. Functioning cells that secrete a variety of other compounds have been reported.

Although it is both exciting and frustrating to attempt to keep abreast of the rapid progress in our knowledge, investigators who worked in the 1950s and early 1960s are delighted that methodology is now available to unravel many puzzling clinical problems associated with "functioning tumors."

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Buffalo, NY 14222

1. Hawfield HH, Daisley GW Jr: A report of a case of a functional adrenal ganglioneuroma. *Clin Proc Child Hosp Washington DC* 8:98-105, 1952.

2. Dicke WK, Kingma BE, Wadman SK, et al: Ganglioneuroma as a cause of diarrhea. Presented at the Ninth International Congress of Paediatrics, Montreal, July 19, 1959.

3. Greenberg RE, Gardner LI: New diagnostic test for neural tumors of infancy: Increased urinary excretion of 3-methoxy-4-hydroxymandelic acid and norepinephrine in ganglioneuroma with chronic diarrhea. *Pediatrics* 24:683-684, 1959.

4. Stickler GB, Hallenbeck GA, Flock EV, et al: Catecholamines and diarrhea in ganglioneuroblastoma. *Am J Dis Child* 104:48-54, 1962.

5. Bloom SR, Polak JM, Pearse AGE: Vasoactive intestinal peptide and watery-diarrhoea syndrome. *Lancet* 2:14-16, 1973.

6. Swift PGF, Bloom SR, Harris F: Watery diarrhoea and ganglioneuroma with secretion of vasoactive intestinal peptide. *Arch Dis Child* 50:896-899, 1975.

7. Pearse AGE, Takor TT: Embryology of the diffuse neuroendocrine system and its relationship to the common peptides. *Fed Proc* 38:2288-2294, 1979.

8. Straus E, Yalow RS: Gastrointestinal peptides in the brain. *Fed Proc* 38:2320-2324, 1979.

9. Voorhess ML: Disorders of the adrenal medulla and multiple endocrine adenomatoses. *Pediatr Cl North Am* 26:209-222, 1979.

Elevated Serum Concentrations of Triiodothyronine in Hypothyroid Patients

Values for Patients Receiving USP Thyroid

Robert Penny, MD, S. Douglas Frasier, MD

• **Serum concentrations of thyroxine (T_4), triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) were measured for 14 hypothyroid patients while they were receiving USP desiccated thyroid and after six weeks of therapy with comparable doses of levothyroxine sodium (Na-*l*-thyroxine). Therapy with USP thyroid caused supraphysiologic elevations in the concentration of T_3 in 13 patients. Treatment with levothyroxine resulted in serum concentrations of T_3 that were within the range of normal. We believe the preferable therapy for hypothyroidism is levothyroxine.**

(*Am J Dis Child* 134:16-18, 1980)

Under physiologic circumstances, the thyroid produces two biologically active hormones: thyroxine (T_4) and triiodothyronine (T_3). The major secreted hormone is T_4, and the primary source of circulating T_3 is monodeiodination of T_4 in peripheral tissues, with backflow of T_3 into the blood. If possible, the therapy for hypothyroidism should imitate this normal physiology. Theoretically, this would be accomplished best by the administration of thyroxine alone, and this has been widely recommended.[1,2] Nevertheless, a substantial number of hypothyroid children continue to receive USP desiccated thyroid.[3] This preparation, which is a mixture of T_4 and T_3, has been shown to produce relatively low concentrations of T_4 and elevated concentrations of T_3 in adult hypothyroid patients.[4-6]

For editorial comment see p 130.

We have systematically investigated the effects of therapy with USP thyroid on serum hormone concentrations in hypothyroidism and have compared these with the effects of therapy with levothyroxine sodium (Na-*l*-thyroxine). Our results show that the treatment of hypothyroidism in childhood and adolescence with USP thyroid is unphysiologic.

SUBJECTS AND METHODS

Fourteen hypothyroid subjects, four male and ten female, ages 6.2 to 18.2 years, were evaluated. They were receiving USP (Armour) thyroid in a dose sufficient to maintain their serum T_4 and thyroid-stimulating hormone (TSH) concentrations within the normal range. At the time this investigation was begun, they had been receiving the dose of USP thyroid given in the Table for periods ranging from 2.7 to 13.0 years. All subjects were clinically euthyroid, and their heights and weights were within normal limits throughout the duration of their therapy. Each subject, at the time of a routine clinic visit, had measurements of T_4, T_3, TSH, and the resin T_3 uptake ratio on the same serum sample. Thyroid therapy was discontinued, and they were given replacement therapy with levothyroxine[7,8] at the dose indicated in the Table. Six weeks after the start of levothyroxine therapy, each subject had repeated determinations of T_4, T_3, TSH, and the resin T_3 uptake ratio on the same serum sample. The methods for these determinations have been previously published.[9-13]

Statistical analysis was performed using both the nonparametric Wilcoxon two-sample rank test and the t test.[14] The P values are two-tailed. Within-group variances are indicated as standard deviations (SDs).

RESULTS

As indicated in the Table, the mean serum T_4 concentration was significantly lower when the patients were receiving USP thyroid than when they were taking levothyroxine sodium (7.6 ± 2.0 μg/dL vs 11.7 ± 2.5 μg/dL; $P < .01$). However, all T_4 values were within the normal range for both treatment regimens. The mean serum concentration of T_3 was greatly elevated during therapy with USP

From the Department of Pediatrics, University of Southern California School of Medicine (Drs Penny and Frasier), Los Angeles; and the Los Angeles County-University of Southern California Medical Center (Drs Penny and Frasier), Los Angeles.

Reprint requests to Los Angeles County-University of Southern California Medical Center, 1801 Marengo St, 2G11, Los Angeles, CA 90033 (Dr Penny).

Results of Tests of Thyroid Function While Receiving USP Desiccated Thyroid and Levothyroxine

Age, yr/Sex	Daily Dosage, USP Thyroid		Hormone Concentrations During Therapy With USP Thyroid*			Daily Dosage, Levothyroxine Sodium		Hormone Concentrations During Therapy With Levothyroxine		
	mg	mg/Kg	T_4, μg/dL	T_3, ng/dL	TSH, μU/mL	μg	μg/kg	T_4, μg/dL	T_3, ng/dL	TSH, μU/mL
6.2/M	97	5.0	11.5	732	0.5	100	5.2	11.8	174	1.9
8.3/M	97	3.5	8.5	483	1.2	100	3.7	14.3	129	1.4
9.3/F	129	4.5	6.8	266	1.4	150	5.2	13.5	160	1.6
10.7/F	129	2.9	4.4	421	1.1	150	3.4	8.9	161	2.2
10.8/F	129	3.4	6.9	315	5.0	150	4.0	14.0	187	1.5
10.8/F	194	5.9	8.0	416	0.5	150	4.6	7.1	176	0.9
11.3/M	194	6.0	8.9	518	2.5	150	4.7	11.0	131	5.0
12.7/F	194	5.2	5.4	229	1.7	150	4.0	6.9	120	1.1
13.4/F	194	3.7	6.7	201	1.1	200	3.8	12.1	130	0.5
13.7/F	129	2.5	7.2	414	1.1	200	3.9	11.3	180	1.8
15.2/M	194	3.5	5.5	284	0.5	200	3.6	11.0	179	1.1
16.7/F	194	4.2	10.7	496	0.5	200	4.3	13.4	169	1.1
17.0/F	194	3.9	6.3	458	0.5	200	4.0	14.0	139	0.5
18.2/F	129	2.5	9.2	265	0.5	200	3.9	14.4	160	1.4
Mean	157	4.1	7.6	393	1.3	164	4.2	11.7†	157†	1.6‡
SD	39.9	1.1	2.0	144	1.2	36.3	0.6	2.5	23	1.1

*Normal range, serum: thyroxine (T_4), 4.2 to 15.0 μg/dL; triiodothyronine (T_3), 70.0 to 220.0 ng/dL; thyroid-stimulating hormone (TSH), 0 to 5 μU/mL.
†When compared with mean of appropriate determination by both the Wilcoxon two-sample rank test and the *t* test during therapy with USP thyroid, $P < .01$.
‡Also using the Wilcoxon two-sample rank test and the *t* test, $P > .1$.

hyroid (393 ± 114 ng/dL vs 157 ± 23 ng/dL; $P < .01$). The USP thyroid herapy resulted in great variability n the serum T_3 concentration, and the serum T_3 value was above the range of normal in 13 of the 14 subjects. Serum TSH concentration was adequately suppressed on both treatment regimens, and there was no difference in TSH concentration when the two therapies were compared.

The resin T_3 uptake ratio, which reflects the serum concentration of thyroxine-binding globulin, was within the normal range on both treatment regimens. While patients received USP thyroid, the ratio was 1.0 ± 0.1 (SD), with a range of 0.9 to 1.2. While patients were being treated with levothyroxine, the ratio was 1.1 ± 0.1 (SD) with a similar range of 0.9 to 1.2.

COMMENT

Previous reports have shown that USP thyroid therapy in hypothyroid adults may be associated with elevated serum concentrations of T_3,[4-6] which may exceed the upper limits of the normal range.[5] A similar phenomenon has been recognized in a few children receiving either USP thyroid[10,15] or thyroglobulin (Proloid).[16] Our results, in a systematically studied group of hypothyroid children, confirm and extend these observations.

One possible explanation for the different effects of these two thyroid hormone preparations on the circulating concentrations of T_4 and T_3 is a discrepancy in equivalent dosage. It has recently been shown that a 1-grain (64.5 mg) tablet of USP thyroid contains approximately 64 μg of T_4 and 12 μg of T_3.[17] Thus, 1 mg of USP thyroid contains 1 μg of T_4 and 100 mg contains 100 μg. In addition, biological equivalence of the two preparations averages 1,000:1; ie, 100 mg of USP thyroid is equivalent to 100 μg of levothyroxine sodium.[6] Thus, the doses of USP thyroid and levothyroxine that our patients received were comparable, both in terms of expected T_4 content and average biological activity. The differences that we observed in the circulating levels of thyroid hormones are functions of the preparations themselves and do not result from a discrepancy in dose.

A difference in the source of thyroid hormones in the circulation offers a more likely explanation for these observations. The USP thyroid extract is prepared from animal thyroid glands as an acetone-dried powder that contains both T_3 and T_4. The T_3 content of porcine[18] and human[19] thyroid glands is quite high, and this is reflected in a relatively high T_3 content in thyroid extract tablets.[17] Thus, when thyroid extract is ingested, the source of serum T_4 is gastrointestinal (GI) absorption and the source of serum T_3 is both GI absorption and peripheral conversion from T_4. A substantial proportion of circulating T_3 represents absorbed hormone. Under these circumstances, the level of T_3 in the serum should be higher than if it were only derived from T_4. This latter circumstance characterizes the ingestion of levothyroxine. When this agent is used, circulating T_4 is derived from GI absorption, and circulating T_3 is only derived from peripheral conversion. The level of T_3 should be relatively low. Differences in GI absorption may explain the lower levels of T_4 when ingested as thyroid extract than when ingested as levothyroxine. Individual variability in absorption, as well as the timing of blood samples relative to a dose of medication, probably account for differences in circulating thyroid hormone levels among individual patients.

The elevated concentrations of T_3 that were present in our patients while they received USP thyroid did not lead to any symptoms or signs of hyperthyroidism. This contrasts with the findings of Jackson and Cobb[5] who observed thyrotoxic symptoms in six of 36 hypothyroid adults in whom serum T_3 concentrations were elevated during therapy with thyroid extract. Symptoms were ameliorated when therapy was changed to levothyroxine. Symptoms of hyperthyroidism have also been reported in the cases of two children receiving USP thyroid[10] and in two receiving thyroglobulin.[16] It is curious that only a minority of patients with elevated serum T_3 concentrations, associated with the administration of USP thyroid or thyroglobulin, had thyrotoxic symptoms and/or signs develop. The reason for this is not readily apparent. One possible explanation might be a variable pattern of serum T_3 levels during the 24 hours after the ingestion of USP thyroid. Previous reports indicated that the T_3 elevations seen after the ingestion of USP thyroid may be transient.[4,5] However, we have no data bearing on this point for our patients.

The results of this study show that the administration of levothyroxine sodium in a single daily dosage of 4.2 ± 0.6 (SD) μg/kg mimics the normal physiology of T_4 secretion and T_3 generation. Replacement therapy with USP thyroid in equivalent amounts leads to severely elevated concentrations of T_3 and is unphysiologic. The long-term effects of such superphysiologic concentrations of T_3 in growing and developing individuals is not known. We believe that our data add additional support to the opinion that the therapy for hypothyroidism with USP thyroid should be abandoned.

Sandra Dills and Wilda Lyons provided secretarial assistance.

Nonproprietary Name and Trademarks of Drug

Thyroglobulin—*Endothyrin, Proloid, Thyractin, Thyrodoids.*

References

1. DiGeorge AM: Disorders of the thyroid gland, in Vaughan VC, McKay RJ (eds): *Nelson Textbook of Pediatrics*, ed 10. Philadelphia, WB Saunders Co, 1975, pp 1301-1318.
2. VanWyk JJ, Fisher DA: Thyroid, in Rudolph AH, Barnett HL, Einhorn AH (eds): *Pediatrics*, ed 16. New York, Appleton-Century-Crofts, 1977, pp 1663-1693.
3. Andersen HJ: Non-goitrous hypothyroidism, in Gardiner LI (ed): *Endocrine and Genetic Disorders of Childhood and Adolescence*, ed 2. Philadelphia, WB Saunders Co, 1975, pp 238-260.
4. Surks MI, Schadlow AR, Oppenheimer JH: A new radioimmunoassay for plasma triiodothyronine: Measurements in thyroid disease and in patients maintained on hormonal replacement. *J Clin Invest* 51:3104-3113, 1972.
5. Jackson IM, Cobb WE: Why does anyone still use desiccated thyroid USP? *Am J Med* 64:284-288, 1978.
6. Sawin CT, Hershman JM, Fernandez-Garcia R, et al: A comparison of thyroxine and desiccated thyroid in patients with primary hypothyroidism. *Metabolism* 27:1518-1525, 1978.
7. Rezvani I, DiGeorge AM: Reassessment of the daily dose of oral thyroxine for replacement therapy in hypothyroid children. *J Pediatr* 90:291-297, 1977.
8. Abbassi V, Aldige C: Evaluation of sodium *l*-thyroxine (T_4) requirements in replacement therapy of hypothyroidism. *J Pediatr* 90:298-301, 1977.
9. Chopra IJ: A radioimmunoassay for measurement of thyroxine in unextracted serum. *J Clin Endocrinol Metab* 34:938-947, 1972.
10. Herbert V, Gottlieb CW, Lau K-D, et al: Adsorption of I^{131}-triiodothyronine (T_3) from serum by charcoal as an in vitro test of thyroid function. *J Lab Clin Med* 66:814-821, 1965.
11. Irvine WJ, Standeven RM: Serum tri-iodothyronine uptake using coated charcoal in the assessment of thyroid function. *J Endocrinol* 41:31-40, 1968.
12. Chopra IJ, Ho RS, Lam R: An improved radioimmunoassay of triiodothyronine in serum: Its application to clinical and physiological studies. *J Lab Clin Med* 80:729-739, 1972.
13. Odell WD, Wilber JF, Paul WE: Radioimmunoassay of thyrotropin in human serum. *J Clin Endocrinol Metab* 25:1179-1188, 1965.
14. Goldstein A: *Biostatistics: An Introductory Text*. New York, Macmillan Publishing Co Inc, 1968, pp 15, 55.
15. Sizonenko PC, Gretillat A, Paunier L: Value of serum thyroxine measurements for the management of congenital hypothyroidism in children. *Helv Paediatr Acta* 33:341-350, 1978.
16. Morillo E, Gardner LI: Hypertriiodothyroninemia in hypothyroidism treated with thyroglobulin. *Am J Dis Child* 133:71-72, 1979.
17. Rees-Jones RW, Larsen PR: Triiodothyronine and thyroxine content of desiccated thyroid tablets. *Metabolism* 26:1213-1218, 1977.
18. Devlin WF, Stephenson NR: The chemical determination of liothyronine and thyroxine in enzymic hydrolysates of pork thyroid. *J Pharm Pharmacol* 14:597-604, 1962.
19. Chopra IJ, Fisher DA, Solomon DH, et al: Thyroxine and triiodothyronine in the human thyroid. *J Clin Endocrinol Metab* 36:311-316, 1973.

Elevated Threshold for Thyrotropin Suppression in Congenital Hypothyroidism

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• Five infants with congenital hypothyroidism were found to have persistently elevated levels of serum thyrotropin (TSH) for six to 24 months after administration of adequate doses of thyroxine. In these infants, the hypothalamic-pituitary threshold for TSH suppression by thyroxine seems to be unusually high. These observations suggest that serum TSH levels should not be the sole criterion for evaluating adequacy of thyroid hormone replacement during the initial months of therapy for congenital hypothyroidism.

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Throughout the latter half of pregnancy, there is progressive maturation of the fetal hypothalamic-pituitary-thyroid axis that is independent of the maternal unit.[1] Consequently, newborn infants with congenital primary hypothyroidism exhibit marked increases in levels of thyroid-stimulating hormone (TSH) and low levels of serum thyroxine (T_4). Traditionally, the dose of thyroid hormone administered to these patients has been adjusted by monitoring both the serum concentrations of T_4 and TSH and by standard clinical criteria.

In a recent publication, congenitally hypothyroid children with thyroid maldescent or athyreosis whose conditions were diagnosed between 6 months and 17 years of age were found to require unusually large doses of thyroxine per kilogram of body weight to block the TSH response to thyrotropin-releasing hormone (TRH).[2] This observation suggested that these patients had an unusually high threshold for TSH suppression by T_4. We studied five infants with congenital hypothyroidism, whose ages at time of diagnosis ranged from birth to 4½ months, and who were found to have persistent elevations of serum TSH levels for six to 24 months after the onset of therapy, even though generous doses of thyroxine were administered and the infants were clinically and biochemically euthyroid.

SUBJECTS AND METHODS

The clinical and laboratory data are given in the Table. Serum T_4 and TSH levels were determined by radioimmunoassay. The interassay coefficient of variation for T_4 was 4.0% and for TSH was 11.2%. All patients were treated from the outset with administration of levothyroxine sodium at dosages ranging from 4 to 11 μg/kg of body weight.

A satisfactory clinical response was based on the disappearance of the physical stigmata of hypothyrodism, documentation of a growth spurt, and restoration of serum T_4 concentrations. All patients were clinically and biochemically monitored at two- to four-month intervals during the first 1 to 2 years of life. Without exception, the infants appeared to be euthyroid within one to two months of starting therapy, and all manifested early and continued acceleration of their linear growth rates. Significant improvement was noted in their intellectual and motor skills and, at the most recent evaluation, the developmental quotients in four infants ranged from 92 to 102. Serum TSH concentration remained elevated for as long as six to 24 months after starting thyroid medication, in spite of clinical and biochemical euthyroidism.

COMMENT

The persistent elevation of TSH levels after adequate thyroid replacement in the congenitally hypothyroid infants described in this report suggests that the hypothalamic pituitary system was relatively unresponsive to the negative feedback effect of thyroid hormone. Sato et al reported that higher doses of T_4 are required to suppress the TSH response to TRH in young children with congenital hypothyroidism.[2] With increasing age, the

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Profile of Patients

Case	Diagnosis	Age at Diagnosis	Age, mo	Levothyroxine Sodium, μg/kg*	Developmental Quotient by Gessell	Thyroxine, μg/dL†	Thyrotropin, μU/mL‡
1	Organ defect	Birth	0	9.0	...	< 1.0	1,760
			2	11.2	...	7.5	180
			4	...	...	9.3	215
			6	7.0	...	9.5	52
			9	...	...	11.3	8
			13	8.8	...	8.3	4
			16	5.0	...	13.6	4
			20	7.5	97	15.0	...
2	Athyreosis	3 mo	3	8.0	...	1.8	256
			9	6.6	...	9.8	...
			13	9.0	...	8.5	70
			16	...	...	11.5	6
			20	6.1	80	12.0	3
			30	...	...	15.2	< 3
			42	5.0	92	12.5	< 3
3	Athyreosis	3 mo	3	9.9	...	< 1.0	210
			6	...	93	13.2	65
			10	...	...	9.1	34
			13	5.0	...	8.4	20
			20	7.0	...	17.4	9
4	Probable athyreosis	4½ mo	4½	4.4	...	< 2.0	520
			5½	...	...	5.7	150
			7	3.9	...	14.8	96
			8½	...	28 wk	12.9	36
			11	5.0	...	10.7	26
			14	5.0	...	8.9	42
			18	6.0	61	10.3	8
5	Lingual thyroid	2 mo	2	6.8	...	< 1.0	736
			6	8.2	93	10.5	39
			9	7.0	...	12.3	13
			13	5.0	...	8.0	29
			17	8.0	102	13.5	7
			24	7.5	...	10.0	35
			32	7.0	...	14.6	19
			38	5.8	...	10.6	8

*Levothyroxine sodium administration started immediately after initial laboratory data.
†Thyroxine normal ranges by age: 3 to 6 months, 8-18 μg/dL; 6 to 12 months, 6-18 μg/dL; > 12 months, 5.0-12.5 μg/dL.
‡Normal thyrotropin level, < 15 μU/mL.

threshold for feedback regulation of TSH decreases in these children. Taken together, these observations suggest that the threshold for TSH suppression by T_4 is high initially, but that the pituitary-hypothalamic centers become increasingly sensitive to the negative feedback effect of thyroid hormones.

The mechanisms that contribute to the early high threshold for TSH suppression in our patients have not been defined. Subresponsiveness of the hypothalamic-pituitary receptors to thyroid hormone is one possibility. Second, long-standing hyperplasia of the thyrotrophs and persistent hypersecretion of TRH and TSH may require prolonged thyroid replacement to establish a normal equilibrium in the hypothalamic-pituitary axis. Third, the lack of fetal thyroid hormone may influence the number and function of the receptors for thyroid hormone in the regulatory centers of the hypothalamus and pituitary.

From a practical standpoint, these observations indicate that during infancy, serum TSH levels cannot be used as the most accurate indicator of adequate thyroid dose. Therapy must be based on age-adjusted normal concentrations of serum T_4, the growth response, and standard clinical criteria. Altering the dose of thyroid hormone to attain TSH suppression places the infant at risk for overtreatment. Our data support the recommendations of the Committee on Drugs of the American Academy of Pediatrics.[3] These precautions do not apply to hypothyroidism acquired during the childhood or adult years, when TSH suppression is an accurate means of monitoring adequacy of thyroid replacement.[4-6]

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References

1. Fisher DA: Thyroid function in the fetus, in Fisher DA, Burrow GN (eds): *Perinatal Thyroid Physiology and Disease*, Kroc Foundation Symposia Series vol 3. New York, Raven Press, 1975, pp 21-32.

2. Sato T, Suzuki Y, Taketani T, et al: Age-related change in pituitary threshold for TSH release during thyroxine replacement therapy for cretinism. *J Clin Endocrinol* 44:553-559, 1977.

3. Segal S, Cohen SN, Freeman J, et al: Treatment of congenital hypothyroidism. *Pediatrics* 62:413-417, 1978.

4. Abassi V, Aldige C: Evaluation of sodium L-thyroxine (T_4) requirement in replacement therapy of hypothyroidism. *J Pediatr* 90:298-301, 1977.

5. Rezvani I, DiGeorge AM: Reassessment of the daily dose of oral thyroxine for replacement therapy in hypothyroid children. *J Pediatr* 90:291-297, 1977.

6. Cotton GE, Gorman CA, Mayberry WE: Suppression of thyrotropin (h-TSH) in serums of patients with myxedema of varying etiology treated with thyroid hormones. *N Engl J Med* 285:529-533, 1971.

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Vasoactive Intestinal Peptide Secreting Tumors of Childhood

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• **A 2-year-old boy with failure to thrive, watery diarrhea, abdominal distention, hypokalemia, metabolic acidosis, and episodes of hypertension and sweating was found to have a calcified right lower quadrant mass. Blood levels of vasoactive intestinal peptide (VIP) and norepinephrine (NE) were elevated. Presurgical management with phenoxybenzamine hydrochloride and metyrosine was associated with an absence of expected postoperative hypotension, and resection of a benign ganglioneuroma resulted in prompt relief of all symptoms and return to normal of VIP and NE levels. Evidence supports the theory that VIP is the substance responsible for the diarrhea that accompanies some neural crest tumors.**

(*Am J Dis Child* 134:21-24, 1980)

Neural crest tumors account for approximately 8% of all malignant pediatric neoplasms.[1] These patients usually have an asymptomatic abdominal, thoracic, or cervical mass

For editorial comment see p 14.

and excessive catecholamine secretion. A minority have flushing, diarrhea, and/or hypertension secondary to neural hormone secretion. Although diarrhea was ascribed to catecholamine excess in the past,[2] it is now believed that vasoactive intestinal peptide (VIP) is the mediator.[3]

We studied a child with chronic diarrhea, acidosis, and hypokalemia secondary to an abdominal ganglioneuroma that secreted excessive quantities of VIP and catecholamines. Preoperative treatment with specific neural hormone antagonists was performed.

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REPORT OF A CASE

A 21-month-old boy was referred for evaluation of watery diarrhea, acidosis, hypokalemia, and abdominal distention of several weeks duration. Physical examination showed a wasted, irritable child with a protuberant abdomen. Blood pressure (supine position) was 80/50 mm Hg. The abdomen was tense and distended, but not tender, and neither ascites nor palpable mass were noted. Height and weight were below the third percentile.

Serum potassium level was 3.0 mEq/L and bicarbonate level was 31 mEq/L. Stools were clay-colored and watery, with a volume of 900 mL/24 hr (1,800 mL/sq m); urinary sodium excretion was 99 mEq/24 hr (normal, 0.5 to 5.0 mEq/24 hr), and potassium excretion was 11 mEq/24 hr (normal, 5.0 to 15.0 mEq/hr). Normal stool trypsin activity, and stool fat, normal glucose, fructose, and sucrose tolerance test results, normal xylose absorption, fat and water-soluble vitamin levels, and sweat chloride determinations were found; and the stools tested negative for reducing substance. A large colon with normal architecture, an enlarged gallbladder, a dilated and kinked right ureter, and nonspecific calcification anterior to the right kidney were identified by roentgenographic techniques.

Diarrhea persisted, even in the absence of oral intake, the serum bicarbonate level fell to 10 to 11 mEq/L, and serum potassium level fell to 2.0 to 2.5 mEq/L. Oral potassium citrate (30 to 50 mEq/24 hr) was given to correct these deficits.

Assay of a 24-hour urine collection showed a vanillylmandelic acid (VMA) level of 68 μg/mg of creatinine (normal, 1.3 to 8.0 μg/mg), a homovanillic acid (HVA)[4] level of 162 μg/mg of creatinine (normal, 4.0 to 23.0 μg/mg), a dopamine level of 4,100 μg/24 hr (normal, 40 to 200 μg/24 hr), and a total catecholamine[5] level of 9.6 μg/mg of creatinine (normal, 0.038 to 0.16 μg/mg). Results of urinary catecholamine fractionation showed 2.3% epinephrine and 97.7% norepinephrine (NE). The serum NE level was 51,000 pg/mL (normal, < 100 pg/mL) and the plasma VIP level was greater than 600 pg/mL (normal, < 80 pg/mL) (Table 1).

Computerized tomography suggested a 4-cm mass anterior to the inferior pole of the right kidney adjacent to the spine (Fig 1). Selective arteriograms were normal, but venography demonstrated a mass partially compressing the inferior vena cava at the level of L-1. Serum NE (venous) value obtained at the level of T-12 was 51,000 pg/mL, and at L-3 was 286,000 pg/mL, suggesting the presence of an intra-abdominal mass not drained by either renal vein (Fig 2).

Because of episodic hypertension (up to 140/100 mm Hg), phenoxybenzamine hydrochloride (an alpha adrenergic blocker), 5 mg orally twice daily, and metyrosine (alpha-methyl-para-tyrosine, a tyrosine hydroxylase inhibitor), 125 mg orally twice daily, were given preoperatively to diminish the possibility of intraoperative hypertension and to avoid postresection hypotension. After five days of therapy with drugs, the urinary total catecholamine level fell (Table 1), and no further episodes of hypertension were noted, but the diarrhea continued.

A small mass was palpated in the midright abdomen with the patient under general anesthesia, and a hard, well-defined, and encapsulated 4-cm tumor was removed from below the right renal vein, adjacent to the inferior pole of the right kidney and right side of the inferior vena cava, and cephalad to the displaced right ureter. Intraoperatively, the patient's blood pressure rose when the tumor was

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manipulated (from 100 to 140 mm Hg systolic). Blood pressure fell (from 100 to 80 mm Hg systolic) when the mass was removed, but returned to the previous level without intervention within 15 minutes. The tumor was a benign ganglioneuroma. Extract of the tumor mass contained VIP levels at greater than 211 ng/g (> 35,000 pg/mL when corrected for 1:100 dilution).

Postoperatively, an immediate cessation of the diarrhea occurred. Several days after removal, the plasma VIP, urine catecholamines, and plasma electrolyte levels had returned to normal. Four months after surgery, the patient remained healthy without evidence of tumor recurrence.

COMMENT

The association of intractable diarrhea with neural crest tumors in childhood was first described by Hawfield and Daisley in 1952.[8] Subsequently, Rosenstein and Engelman[9] reported a 9% incidence of diarrhea in pediatric patients with neural crest tumors. A similar syndrome in adults with non-β islet cell tumors of the pancreas was described in 1958 and later reviewed in 1974 by Verner and Morrison.[10,11] Since that time, the syndrome of watery diarrhea, hypokalemia, and achlorhydria (WDHA) has been described in adults with pancreatic tumors, pancreatic hyperplasia, bronchogenic carcinoma, hepatic failure, pheochromocytoma, and ganglioneuroblastoma.[6] Vasoactive intestinal peptide is produced by these tumors and is the proposed mediator of this syndrome.[3] It induces increased electrolyte and water secretion by gastrointestinal mucosal cells through stimulation of the adenyl cyclase system.[12] Vasoactive intestinal peptide also causes hyperglycemia, hypercalcemia, inhibition of gastric acid secretion, and profound vasodilatation leading to flushing and hypotension.[11]

Ganglioneuroma and ganglioneuroblastoma are the only tumors reported to produce VIP in children. Eight cases have now been reported and age, sex distribution, histology, location of primary site, blood pressure status, hormone levels, and associated findings are summarized in Table 2. Levels of VIP were elevated in all, but were not as high as those noted in adults. However, tumor tissue levels were comparable.[6] Complete excision was possible and postoperative cessation of symptoms occurred in all but three cases. In one of the unresected cases, the site of VIP production was never found and the child subsequently died of sepsis.[15] A second experi-

Table 1.—Monitored Parameters

	Total Urine Catecholamines, μg/mg of Creatinine	Plasma Vasoactive Intestinal Peptide, pg/mL	Blood Pressure, mm Hg
Baseline	9.6	> 600	80-140/50-100
After five days of therapy with metyrosine	0.63	340	80-90/50
Postoperative	0.016	70	80/50
Normal (for age)	0.038-0.16	< 80	70-105/30-65[7]

Fig 1.—Computerized tomogram of the abdomen suggesting a 4-cm paraspinal mass anterior to the inferior pole of the right kidney (arrows), located at the level of the first lumbosacral vertebra.

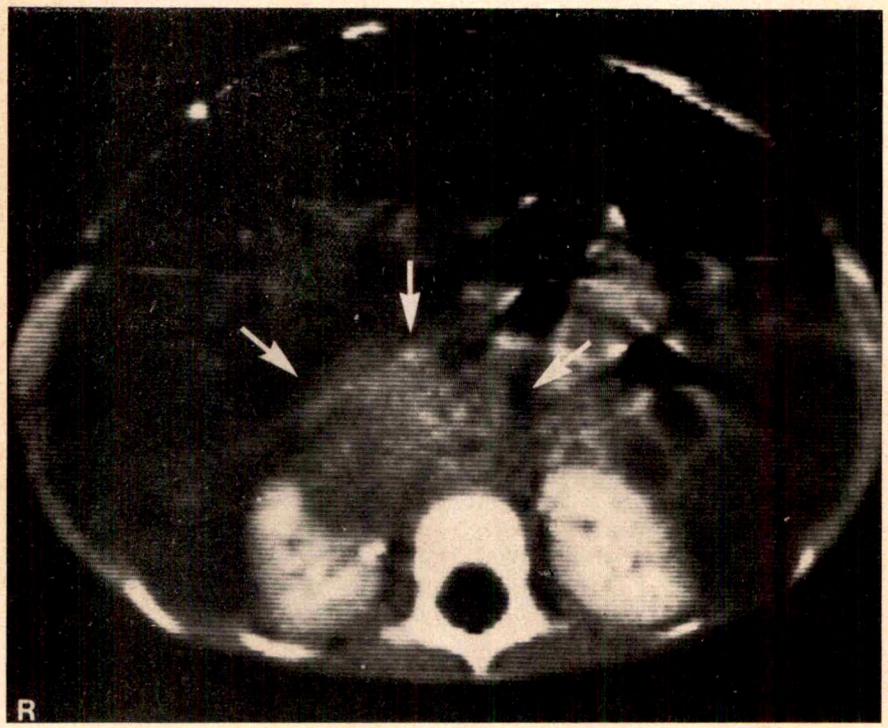
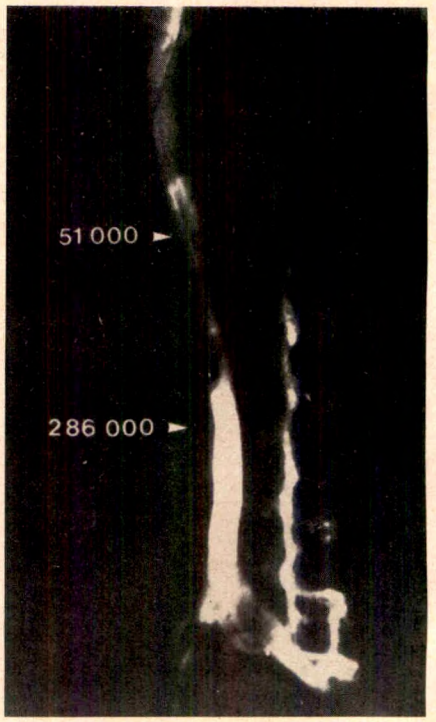


Fig 2.—Venogram demonstrating a right-sided extrinsic compression defect of the inferior vena cava at L-1, with serum norepinephrine levels obtained at T-12 and L-3 (in pg/mL).



enced cessation of diarrhea with partial resection of a ganglioneuroma,[14] and a third died from metastatic ganglioneuroblastoma while undergoing chemotherapy.[18]

Diarrhea is the most common initial complaint in children with VIP-secreting tumors. Hypokalemia and abdominal distention are also frequently found and the hypokalemia is believed to result from massive fecal loss of potassium.[16] These findings are similar to those reported in a review of 18 children with diarrhea and neurogenic tumors in 1963 before the discovery of VIP.[9] Less common signs are failure to thrive and gallbladder distention. Hypercalcemia and glucose intolerance are present in more than 50% of all adults with VIP excess,[11] but similar findings, to our knowledge, are not described in the reported childhood cases.

The catecholamine elevation present in six of the cases reviewed reflects the origin of these tumors from neural tissue. Although concurrent increased secretion of catecholamines and VIP has been reported in an adult with ganglioneuroblastoma,[20,21] catecholamine excess is not generally demonstrated in the more common pancreatic and bronchogenic VIP-secreting tumors.[6,11] The common occurrence of catecholamine excess in children and its rarity in adults with VIP-secreting tumors may explain some of the differences between the presentation of these tumors in these two groups.

Before the discovery of VIP, catecholamines were believed to cause the diarrhea associated with neurogenic tumors.[2,9] However, this hypothesis did not adequately explain why the majority of patients with elevated catecholamine levels have no diarrhea or why some patients with neural crest tumors have diarrhea and normal catecholamine values.[22] It also did not adequately explain why, in a child with watery diarrhea and elevationed levels of both VIP and urinary catecholamines, diarrhea ceased when VIP levels dropped to normal after partial resection of a ganglioneuroma although catecholamine elevation persisted.[14] The summary of present evidence suggests that the diarrhea associated with neural crest tumors is a symptom produced by VIP excess and not by catecholamines.[3,6,12]

Although extensive investigation into the individual effects of VIP and catecholamines has been carried out, there has been little work on the combined effects of these agents. Norepinephrine causes vasoconstriction, whereas VIP is a potent vasodilator. It has been suggested that normotension in some patients with elevations of both hormones is due to these opposing actions.[20,21] However, in cases of VIP elevation alone, hypotension does not usually occur, nor does hypertension always accompany catecholamine excess. In patients with pheochromocytoma, decreased intravascular volume and diminished catecholamine receptor sensitivity are believed to compensate in part during the extreme catecholamine excess and thus avoid continuous extreme hypertension.[23] Consequently, when these tumors are removed and catecholamine levels fall, severe hypotension can occur.

Modlin et al[20] and Taylor et al,[21] describing the same patient, reported near fatal hypotension in an adult after resection of a ganglioneuroblastoma containing both VIP and NE. Intraoperative VIP and NE determination showed more rapid clearance of NE that left a sudden elevation of VIP alone, which corresponded with the onset of hypotension. This is not unlike the hypotension that occurs after resections of a pheochromocytoma. Whether the presence of VIP affects the severity of the hypotension has not been determined.

Our patient had very high levels of NE and intermittently showed signs of catecholamine excess (hypertension

Table 2.—Vasoactive Intestinal Peptide (VIP) Secreting Tumors of Childhood*

Source	Age, yr/ Sex	Type, Location	Urine Catechol-amines	VIP Plasma, pg/mL	VIP Tissue, μg/g	Blood Pressure	Findings, Other than Diarrhea
Swift et al[14]	5/F	GN, thorax (incomplete resection)	Increased	292	3.6	Increased	Abdominal distention
Udall et al[15]	7½/M	Tumor not found	Normal	700	NR	NR	Flushing, failure to thrive, hypokalemia
Mitchell et al[16]	1½/F	GNB, abdomen	Increased	450	43	NR	Abdominal distentions, hypokalemia
Jansen-Goemans and Engelhardt[13]	1/F	GNB, neck	Increased	645	0.368	Increased	Abdominal distention, hypokalemia
Leupold et al[17]	2½/M	GN, thorax	Normal	Elevated	0.540	NR	Hypokalemia, gallbladder enlarged
Ricour et al[18]	½/M	GNB, paraspinal (thorax and abdomen)	Increased	600	NR	Normal	Abdominal distention, hypokalemia failure to thrive, bone metastases
Fontaine et al[19]	2½/F	GN, thorax (dumbell tumor)	Increased	Elevated	3.5	Normal	Hypokalemia, paraplegia
Present case	2/M	GN, abdomen	Increased	> 600	> 0.211	Increased	Abdominal distention, failure to thrive, hypokalemia, gallbladder enlarged

*GN indicates ganglioneuroma; GNB, ganglioneuroblastoma; NR, not recorded.

and sweating). Postresection hypotension was therefore expected due to rapid cessation of catecholamine secretion and transient persistence of VIP in the plasma.[21] To avoid this complication, the patient was treated preoperatively with phenoxybenzamine and metyrosine to reduce pharmacologically the catecholamine levels, block their vasoconstricting actions, and restore intravascular volume.[24] Our patient's blood pressure did not drop preoperatively despite a severe reduction in catecholamine secretion and continued elevation of VIP. The blood pressure, likewise, remained normal after removal of his hormone-secreting tumor. Thus, it appeared that the normal blood pressure in our patient was not simply a result of the balance between these two mediators, but perhaps involved more complex compensatory mechanisms.

The VIP levels in this case fell with administration of metyrosine, although less than did the NE level. Metyrosine is an amino acid analog and may interfere with the synthesis of the tyrosine-containing octocosapeptide VIP. However, catecholamines alone may affect the secretion of VIP, as they are known to stimulate the release of other hormonal products (eg, beta-adrenergic mediated release of insulin). Hence, by diminishing catecholamine levels, VIP release may have been secondarily reduced. In our case, therapy with metyrosine was instituted for only five days prior to VIP measurement. It is likely that longer use of metyrosine could have suppressed VIP levels to the point of diminishing the associated symptoms (ie, diarrhea). Metyrosine is a relatively safe drug whose only untoward effects are sedation (with insomnia on withdrawal), anxiety, tremor, diarrhea, and galactorrhea.[24] A therapeutic trial appears appropriate for any patient with a nonresectable neurogenic tumor and intractable symptoms.

The VIP-producing tumors in children have a somewhat different presentation from the WDHA syndrome as described in adults. Watery diarrhea, hypokalemia, and abdominal distention are common findings. Additionally, symptoms and signs of excess catecholamine secretion such as flushing, increased sweating and hypertension are frequently present. Hyperglycemia and hypercalcemia, although frequently seen in adults with increased VIP secretion, have not been noted in children.

Measurement of VIP should be included in the evaluation of chronic diarrhea after the more usual causes have been ruled out. If VIP level is elevated in a child, a neural crest tumor should be located and removed. Catecholamine levels should also be measured to determine whether preoperative antiadrenergic therapy might be useful. Finally, metyrosine may be useful in the symptomatic treatment of patients with VIP excess.

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References

1. Sutow W, Vietti T, Fernbach D: *Clinical Pediatric Oncology*, ed 2. St Louis, CV Mosby Co, 1977, p 3.

2. Scully RE, McNeily BU: Weekly clinicopathological exercises. *N Engl J Med* 291:1351-1355, 1974.

3. Bloom SR, Polak JM, Pearse AGE: Vasoactive intestinal peptide and watery diarrhea syndrome. *Lancet* 2:14-16, 1973.

4. Sprinkle TJ, Porter AH, Greer M, et al: An improved method for the determination of homovanillic acid and vanillylmandelic acid by gas chromatography. *Clin Chim Act* 25:409-411, 1969.

5. Kissinger PT, Riggin RM, Allcorn RL, et al: Estimation of catecholamines in the urine by high performance liquid chromatography with electrochemical detection. *Biochem Med* 13:299-306, 1975.

6. Said SI, Faloona GR: Elevated plasma and tissue levels of vasoactive intestinal peptide in the watery diarrhea syndrome due to pancreatic, bronchogenic and other tumors. *N Engl J Med* 293:153-160, 1975.

7. Voors AW, Webber LS, Berenson GS: A consideration of essential hypertension in children. *Pract Cardiol* 3:29-40, 1977.

8. Hawfield HH, Daisley CW: A report of a case of a functional adrenal ganglioneuroma. *Clin Proc Child Hosp* 8:98-105, 1952.

9. Rosenstein BJ, Engelman K: Diarrhea in a child with a catecholamine secreting ganglioneuroma. *J Pediatr* 63:217-226, 1963.

10. Verner JV, Morrison AB: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. *Am J Med* 25:374-380, 1958.

11. Verner JV, Morrison AB: Non-beta islet tumors and the syndrome of watery diarrhoea, hypokalemia and hypochlorhydria. *Clin Gastroenterol* 3:595-606, 1974.

12. Schwartz CJ, Kimberg DV, Sheerin HE, et al: Vasoactive intestinal peptide stimulation of adenylate cyclase and active electrolyte secretion in intestinal mucosa. *J Clin Invest* 54:536-544, 1974.

13. Jansen-Goemans A, Engelhardt J: Intractable diarrhea in a boy with vasoactive intestinal peptide producing ganglioneuroblastoma. *Pediatrics* 59:710-716, 1977.

14. Swift PGF, Bloom SR, Harris F: Watery diarrhea and ganglioneuroma with secretion of vasoactive intestinal peptide. *Arch Dis Child* 50:896-899, 1975.

15. Udall JN, Singer DB, Huang CTL, et al: Watery diarrhea and hypokalemia associated with increased plasma vasoactive intestinal peptide in a child. *J Pediatr* 88:819-821, 1976.

16. Mitchell CH, Sinatra FR, Crast FW, et al: Intractable watery diarrhea, ganglioneuroblastoma and vasoactive intestinal peptide. *J Pediatr* 89:593-595, 1976.

17. Leupold D, Rosch U, Zollner E, et al: Chronische Diarrhoe, Ganglioneurom und vaso-active intestinal Polypeptide (VIP). *Monatsschr Kinderheilkd* 125:462-463, 1977.

18. Ricour C, Duhamel JF, Lesec G, et al: Diarrhee choleriforme dans un cas de ganglioneuroblastome. *Arch Fr Pediatr* 34:552-555, 1977.

19. Fontaine JL, Giardet JP, Bataille D, et al: Sympathome et diarrhee par hypersecretion de "Vasoactive Intestinal Peptide" (VIP): A propos d'une nouvelle observation. *Arch Fr Pediatr* 34:577-578, 1977.

20. Modlin IM, Bloom SR, Barnes A, et al: Cure of intractable watery diarrhoea by excision of vipoma. *Br J Surg* 65:234-236, 1978.

21. Taylor AR, Chaljata D, Jones DH, et al: Adrenal tumor secreting vasoactive intestinal peptide and noradrenalin. *Anesthesia* 32:1012-1016, 1977.

22. Peterson HD, Collins OD: Chronic diarrhea and failure to thrive secondary to ganglioneuroma. *Arch Surg* 95:934-936, 1967.

23. Sabiston DC (ed): *David-Christopher Textbook of Surgery*, ed 11. Philadelphia, WB Saunders Inc, 1977, pp 739-790.

24. Engelman K, Horwitz D, Jequiet E, et al: Biochemical and pharmacologic effects of alpha-methyltyrosine in man. *J Clin Invest* 47:577-594, 1968.

Computerized Tomography in the Evaluation of Isosexual Precocity

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• Clinical and laboratory observations were made in three children with isosexual precocity. None of the patients showed abnormalities in neurological or visual-field examinations although one patient had arrested hydrocephalus and a head circumference greater than the 98th percentile for her age and another patient had a history of seizures. Roentgenograms of the skull were normal in all patients. Cranial computerized tomography (CT) identified a lesion in each patient. We believe that cranial CT should be performed in any patient with isosexual precocity in whom a specific cause is not evident or in whom a cerebral cause is suggested even though the patient may be otherwise normal. Cranial CT is a safe, accurate, and noninvasive technique.

(*Am J Dis Child* 134:25-27, 1980)

The onset of pubertal change prior to 8 years of age in a girl and prior to 10 years of age in a boy is considered to constitute sexual precocity.[1] Although there are many causes to be considered, sexual precocity is not an uncommon sign of an intracranial neoplasm.

Computerized tomography (CT) is a new, safe, and noninvasive roentgenographic technique that has been used to diagnose intracranial abnormalities in infants and children.[2-5] Importantly, CT is without the risks of pneumoencephalography or cerebral angiography.

We describe here three children with isosexual precocity seen during a six-month period, in whom the etiology of the sexual precocity was first detected by cranial CT. Pneumoencephalography and cerebral angiography were used subsequently to further define the lesion and its vascular nature.

REPORT OF CASES

CASE 1.—A boy 6 years and 2 months of age was referred because of pubertal development. He experienced normal development until one year prior to admission when enlargement of the penis and presence of pubic hair were first noted by the parents. Acne and a deepening of the voice had been present for six months. His linear growth from birth to 7 months of age was at the 25th percentile. At 25 months of age, his height was at the 90th percentile. No other growth records were available. The patient had no symptoms referable to the CNS. There was no family history of sexual precocity and there was no history of hormone ingestion.

Physical examination provided the following information: height, 135 cm (greater than the 95th percentile for age); weight, 35.5 kg; blood pressure, 100/60 mm

Blood Hormone Studies

Hormone*	Serum Hormone Values in Cases 1	2	3	Normal Prepubertal Values†
FSH, ImU/mL	5.7	11.2	15	2-11
LH, ImU/mL	13.7	11.3	8	< 6
Testosterone, ng/dL	299	...	...	< 10
17-OH Progesterone, ng/dL	34	...	...	3-90
Androstenedione, ng/dL	67	...	...	8-50
Total estrogens, ng/dL	...	7.1	14.7	< 5
Estrone, ng/dL	...	2.3	...	< 1
Estradiol, ng/dL	...	4.5	10.3	< 1

*FSH indicates follicle-stimulating hormone; LH, luteinizing hormone.
†Normal values established by Endocrine Sciences, Tarzana, Calif.

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Hg; and pulse rate, 80 beats per minute. The voice was deep and moderate acne was present on the face. Pubic hair growth and genital development were both Tanner stage 4. Each testis had a volume of 15 mL. The expected testicular volume at this age is between 2 and 4 mL.[4] Neurological and visual-field examinations showed no abnormalities.

Hemogram and urinalysis results were normal. The bone age was 12 years. Roentgenograms of the skull were normal. Results of the patient's hormone studies are given in the Table. The CT scan showed a solid mass that involved the suprasellar cistern (Fig 1), which was not defined further after administration of contrast medium. Angiography confirmed the presence of the mass and the vascular nature of the tumor. Pneumoencephalography demonstrated the mass with its displacement of the surrounding structures.

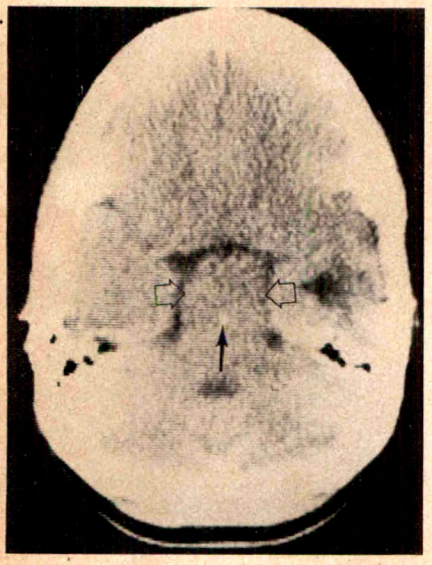

Fig 1.—Solid mass involves suprasellar cistern (open arrows). Basilar artery (solid black arrow) lies directly in front of pons. Normally, there should be CSF (prepontine and suprasellar cisterns) anterior to basilar artery (case 1).

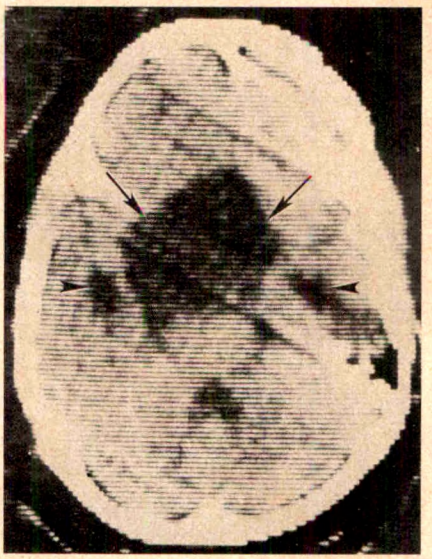

Fig 2.—Large CSF-density cyst (arrows) and mild dilation of temporal horns (arrowheads) (case 2).

Fig 3.—This cut through frontal horns demonstrates that cyst (black arrows) is separated from frontal horns by thin membrane (white arrows) (case 2).

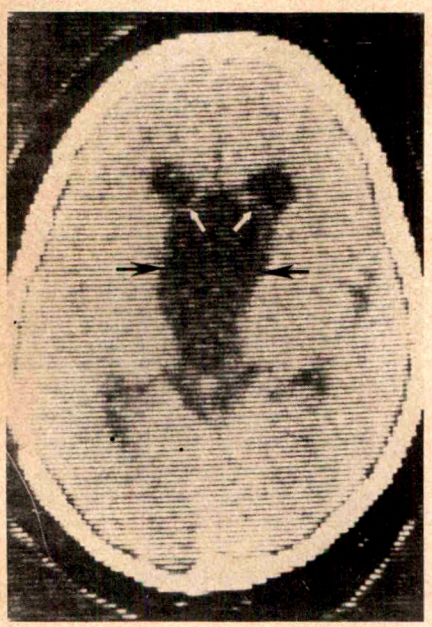

Fig 4.—Cerebrospinal fluid-density suprasellar cyst (arrowheads). Cyst could be confused with third ventricle (case 3).

At surgery, a hypothalamic glioma that originated from the area of the tuber cinereum was found and partially removed. The patient at 7 years and 11 months of age now has a height of 146.4 cm and a weight of 49.8 kg. He is at stage 5 of sexual development. Neurological examination shows no abnormalities.

Case 2.—A girl 5 years and 9 months of age was seen because of seizures and breast development. She was in good health until eight months prior to admission when she experienced her first tonoclonic convulsion. Breast development was first noted at this time. The patient was visiting Washington, DC when she experienced her second convulsion. There was no family history of sexual precocity or of hormone ingestion.

Physical examination provided the following information: height, 111.5 cm (25th to 50th percentile for age); weight, 23 kg; blood pressure, 100/80 mm Hg; and pulse rate, 86 beats per minute. Breast development was Tanner stage 3. No acne or axillary or pubic hair was present. There were no café au lait spots present. The labia minora were pigmented and the vaginal mucosa was pink. On rectal examination, the right ovary was enlarged and the left ovary was barely palpable. Neurological and visual-field examinations showed no abnormalities.

Hemogram and urinalysis results were normal. The bone age was 9 years. Roentgenograms of the skull were normal. An EEG showed an active epileptogenic focus in the left midtemporal area. The results of blood hormone studies are listed in the Table.

The CT scans demonstrated a suprasellar cyst with a density comparable to CSF. Minimal hydrocephalus was also present (Fig 2 to 3). Pneumoencephalography and cerebral angiography confirmed the presence of the mass and showed no evidence of neovascularity.

At surgery, a left temporal arachnoid cyst that extended into the suprasellar area across the midline was found and excised. The patient was lost to follow-up after surgery when she returned to her home in another city.

Case 3.—A girl 7 years and 11 months of age had been followed up for the preceding three years because of arrested hydrocephalus. Breast development had been present

for three months and pubic hair was noted one week prior to referral. There had been no unusual growth acceleration. There was no family history of sexual precocity or of hormone ingestion.

Physical examination provided the following information: height, 141.5 cm (greater than the 80th percentile for age); head circumference, 56 cm (greater than the 98th percentile for age); weight, 39.2 kg; blood pressure, 90/40 mm Hg; and pulse rate, 80 beats per minute. Breast development was Tanner stage 3 and pubic hair growth was Tanner stage 2. The labia minora were pigmented and the vaginal mucosa was pink. The ovaries were not palpable on rectal examination. There was no abnormal cutaneous pigmentation present. Neurological and visual-field examinations showed no abnormalities.

Hemogram and urinalysis results were normal. The bone age was 11 years. Skull roentgenograms were normal. The results of blood hormone studies are given in the Table. The CT scans were similar to those obtained in case 2 except the cyst was smaller and the hydrocephalus was more severe (Fig 4). Cerebral angiography demonstrated that the mass was avascular. Pneumoencephalography demonstrated that the cyst was partially filled with air and thus defined its subarachnoid connection. At surgery, a large suprasellar arachnoid cyst was found and excised.

Menarche occurred at 9 years and 11 months of age and the patient's menstrual periods have been regular. At 10 years and 11 months of age, her height was 156.4 cm and weight was 45.4 kg. She was at stage 4 of sexual development. Results of neurological examination remained normal.

COMMENT

True isosexual precocity is due to premature activation of the hypothalamic-pituitary-gonadal axis that leads to increased circulating levels of the gonadotropins and sex hormones. True isosexual precocity may be separated into "cerebral" and "idiopathic" types.

The cerebral type includes isosexual precocity associated with an identifiable lesion in the brain such as tumor in or adjacent to the hypothalmus, hydrocephalus, or neurofibromatosis.[1] In the absence of an identifiable lesion, the true isosexual precocity is classified as idiopathic. Idiopathic true isosexual precocity is diagnosed by exclusion. True isosexual precocity is more common in girls than in boys, with a sex ratio of approximately 3:1.[5] The idiopathic type is about nine times more frequent than the cerebral type in girls, whereas the ratio is only about 1.5:1 in boys.[5] It should be remembered that in some cases where conditions were diagnosed as idiopathic sexual precocity, there have been cerebral lesions found many years later or detected at postmortem examinations.[6] Therefore, the true incidence of idiopathic isosexual precocity is not known.

Four girls and one boy were studied and their conditions diagnosed as idiopathic isosexual precocity during the six-month period in which our three patients with cerebral isosexual precocity were seen. The incidence of idiopathic vs cerebral type of isosexual precocity based on CT scans in our patients cannot be accurately compared with the incidence reported by Reiter and Kulin[5] because of the small number of patients we saw.

A most difficult differential diagnosis, especially when neurological abnormalities are not evident, is between idiopathic sexual precocity and that owing to an intracranial lesion. Gonadotropin and sex hormone levels are much the same in both types[5] and are, therefore, of no diagnostic help in the differentiation.

We have previously emphasized that pneumoencephalography is mandatory in any boy with isosexual precocity in whom no specific cause can be determined.[7] Pneumoencephalography has been recommended in the evaluation of girls with sexual precocity only if neurological evaluation indicates an abnormality.[5] This suggestion has been made because of the much lower reported incidence of cerebral as compared with idiopathic type of sexual precocity in girls as well as because of the risks of pneumoencephalography.

Based on our experience, we believe that cranial CT is essential in any girl or boy with isosexual precocity in whom no specific cause can be determined or in whom a cerebral cause is suggested. Cranial CT is a safe, accurate, and noninvasive technique and is without the attendant risks of pneumoencephalography or cerebral angiography. The latter two techniques may be necessary to further define the lesion if CT scans show the presence of a lesion.[2]

References

1. Wilkins L: *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, ed 3. Springfield, Ill, Charles C Thomas Publishers, 1965, pp 225-227.

2. Harwood-Nash DC, Fitz CR, Reilly BH: Cranial computed tomography in infants and children. *Can Med Assoc J* 113:546-549, 1975.

3. Gomez MR, Reese DF: Computed tomography of the head in infants and children. *Pediatr Clin North Am* 23:473-498, 1976.

4. Zachmann M, Prader A, Kind HP, et al: Testicular volume during adolescence. *Helv Pediatr Acta* 29:61-72, 1974.

5. Reiter EO, Kulin HE: Sexual maturation in the female: Normal development and precocious puberty. *Pediatr Clin North Am* 19:581-603, 1972.

6. Van der Werff ten Bosch JJ: Isosexual precocity, in Gardner LI (ed): *Endocrine and Genetic Diseases of Childhood and Adolescence*, ed 2. Philadelphia, WB Saunders Co, 1975, pp 616-639.

7. Hung W, Milhorat TH, Nelson KB, et al: Sexual precocity as the only sign of a brain tumor in a 9-year-old boy. *Am J Dis Child* 121:524-527, 1971.

Pneumonia During Therapy for Childhood Acute Lymphoblastic Leukemia

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• The incidence of pneumonia was evaluated in 844 children undergoing initial treatment for acute lymphoblastic leukemia (ALL). A total of 310 episodes occurred in 239 patients followed up for five to 36 months after diagnosis. The peak incidences occurred in the periods 0 to 20 days and 40 to 80 days after the start of antileukemic therapy. Bacterial pneumonias occurred primarily during the first 20 days after diagnosis of ALL. No episode of *Pneumocystis carinii* pneumonia was noted before 40 days, and the majority of instances occurred 50 to 120 days after diagnosis. In 80% of all episodes, a specific causative organism was not detected. The incidence of *P carinii* pneumonia was greater in patients receiving intrathecal methotrexate as part of CNS prophylaxis than in those receiving only CNS irradiation. Pneumonia is a frequent event during the therapy of ALL in childhood.

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Pulmonary infections frequently occur during the therapy of acute leukemia and other malignancies of the hemopoietic system, often resulting in interruption of intensive chemotherapy programs and/or in death.[1-7] According to the literature, pneumonia accounts for 28% to 43% of all fatal and nonfatal infections in these patients.[1,5] Bacterial and fungal organisms comprise more than 90% of all the documented etiologic agents, although viruses and protozoans are recovered more frequently than from normal age-matched patient populations[1-3] and are the most common causes of death due to pneumonia in some series.[6] In addition, the direct pulmonary effects of radiation and specific chemotherapeutic agents, such as methotrexate, have been increasingly implicated in these processes as they are incorporated into standard treatment regimens for acute leukemia.[8-19]

Previous studies of pulmonary disease in acute leukemia have consisted of investigations that stress severe or fatal episodes in relatively small patient populations.[1,2,6,7,20] To determine the frequency and characteristics of pulmonary disease during the therapy of childhood acute lymphoblastic leukemia (ALL) in a large representative population and to identify factors contributing to the development of pulmonary complications, an evaluation was conducted by the Childrens Cancer Study Group (CCSG) as an integral part of an ongoing treatment program for childhood ALL.

SUBJECTS AND METHODS

Patient Population

All patients aged birth to 16 years entered on CCSG protocols 101 and 143 were eligible for this study. Three standard phases of therapy are identified for both protocols: induction, intensification, and maintenance. Protocol CCSG-101 (Fig 1) was designed, in part, to determine the most effective and least toxic means of controlling extramedullary disease in ALL by randomizing patients who attain bone-marrow remission status to one of four intensification regimens, as follow: regimen 1, craniospinal irradiation 2,400 rads and 1,200 rads to an "extended" field that includes total abdomen and pelvis (the testes are included in the pelvic field); regimen 2, craniospinal irradiation 2,400 rads; regimen 3, cranial irradiation 2,400 rads plus methotrexate 12 mg/sq m intrathecally (IT) twice weekly for a total of six doses; and, regimen 4, methotrexate 12 mg/sq m IT twice weekly for six doses only. All patients younger than 18 months of age at the time of diagnosis were assigned to regimen 4. After completion of the intensification phase, a four-drug maintenance program was used, including daily administration of oral mercaptopurine, weekly administration of oral methotrexate, and monthly "pulses" of vincristine sulfate and prednisone.

Protocol CCSG-143 followed this study to test the effectiveness of using a radiation dose of 1,800 rads for CNS prophylaxis. Patients in this study received the same induction and maintenance schedules as those described for CCSG-101, but were

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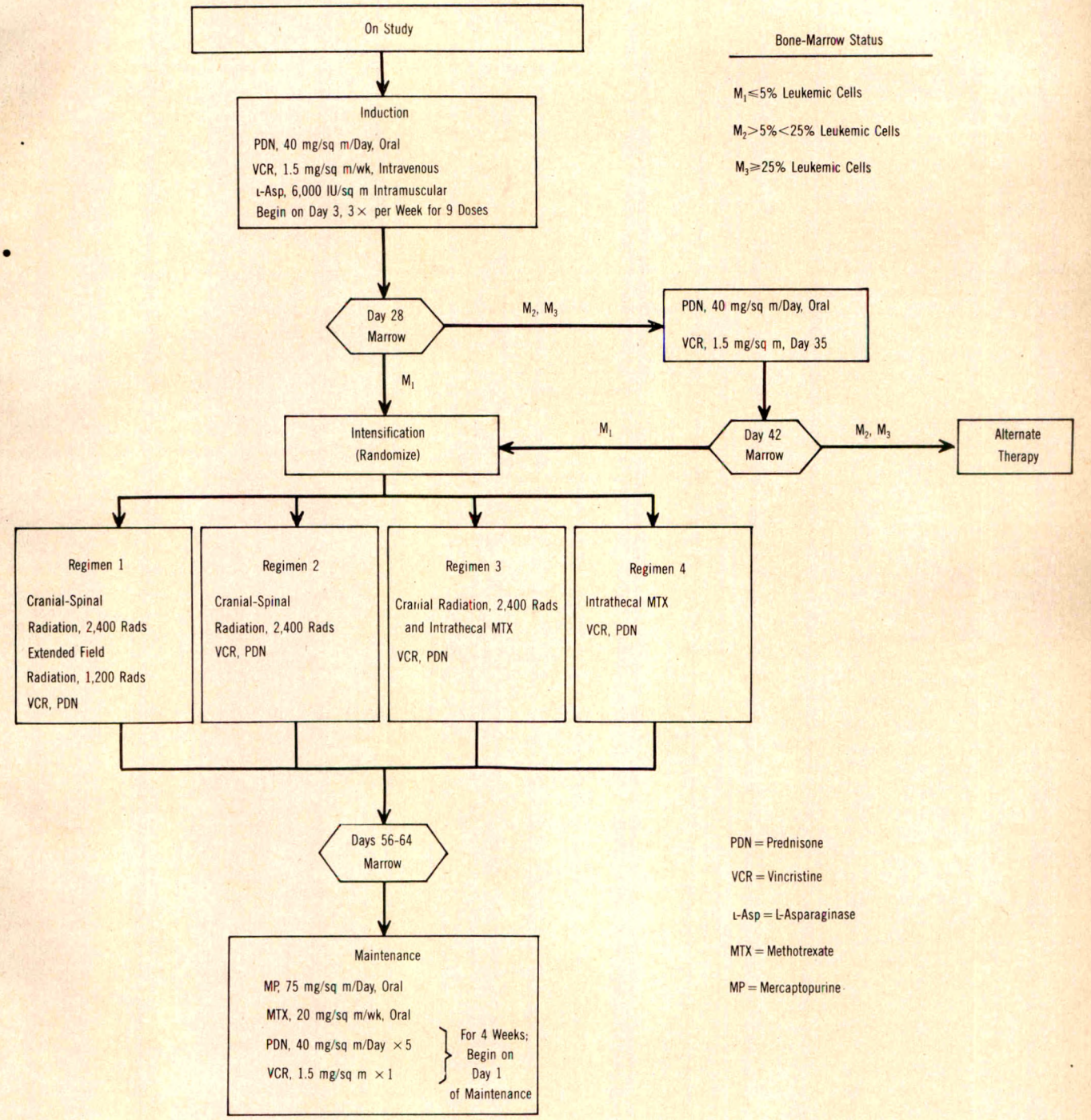

Fig 1.—Therapeutic design for CCSG-101 protocol for acute lymphoblastic leukemia (ALL).

randomized in the intensification phase only to regimens 2 and 3 of CCSG-101. The dose of radiation in both remaining treatment regimens was reduced to 1,800 rads. Infants younger than 18 months of age at time of diagnosis again received IT methotrexate only. Patients were considered "off study" when bone marrow relapse (M_3) occurred or an initial bone-marrow remission (M_1) was not obtained after six weeks of induction therapy. Thus, data presented in this report represent only those events occurring during the initial induction period and first remission of children with ALL.

From June 1972 to February 1975, 844 consecutive patients with ALL were entered on the two treatment programs; 20 institutions in the CCSG were represented. Patients were followed up continually while on study for periods of up to 36 months, with 74% having at least a six-month follow-up and 60% a minimum of a one-year follow-up. For the purpose of the present report, the patient populations of the two studies (CCSG-101 and CCSG-143) were combined and tabulated by intensification regimens. No major statistical differences in identifiable "front-end" prognostic disease variables, such as age and initial WBC count, were noted between the two study groups.

Study Techniques

A detailed questionnaire was completed by investigators at participating institutions on any patient entered on the CCSG-101 or CCSG-143 programs in whom evidence of pneumonia developed. For the purpose of this study, pneumonia was defined as the appearance of a new pulmonary infiltrate on diagnostic roentgenogram accompanied by *one or more* clinical symptom, including fever, cough, tachypnea, cyanosis, and chest pain. Episodes separated by a minimum of seven asymptomatic days were considered to be separate occurrences. Episodes of documented pulmonary embolus were excluded unless proved to be due to infectious agents, such as *Aspergillus* sp. All patients were evaluated for episodes of pneumonia with a complete physical examination and chest roentgenogram. Additional diagnostic studies were performed according to current clinical practices of the participating institution and were not specified in this study protocol.

The questionnaire was designed to determine the clinical, roentgenographic, and laboratory findings accompanying each episode, time of onset in relation to duration of ALL therapy, CNS intensification regimen used, microbiological isolates from diagnostic cultures, clinical course, and ultimate outcome.

Table 1.—Cause of Pneumonia Episodes (N = 310)

Documented Cause	Cases (% of Total)
Bacterial and/or fungal*	
Staphylococcus aureus	8
Streptococcus pneumonia	3
Escherichia coli	4
Pseudomonas aeruginosa	1
Klebsiella sp	1
Aspergillus sp	1
Subtotal	**18 (5.8)**
Viral	
Herpes zoster	4
Cytomegalovirus	1
Adenovirus	1
Rubeola	2
Subtotal	**8 (2.5)**
Pneumocystis carinii†	22 (6.8)
Interstitial pneumonia	8 (2.6)
Leukemic infiltration	1 (0.3)
Undetermined	248 (80.3)
Not evaluable	5 (1.6)

*Three mixed. infections: one episode each with *E coli* plus *Salmonella* sp; *S aureus* plus *Herpesvirus parainfluenzae*; and, *Klebsiella* sp plus unidentified viral agent.

†Two mixed infections: one episode each with associated E *coli* and *H influenzae*.

Statistical Methods

A computer file was created, using the data abstracted from the pulmonary disease questionnaires, that documented each episode of pneumonia occurring before June 1, 1975. The data in this file were then linked to the basic patient data files maintained for all patients in studies CCSG-101 and CCSG-143. Because patients were under observation for varying periods of time, the method of patient days at risk was used to standardize the majority of the calculated pneumonia incidence rates and comparisons. Life-table comparisons were calculated using the Mantel-Peto-Cox summary χ^2 statistic.[21]

RESULTS

Incidence of Pneumonia

In the 844 patients studied, a total of 310 episodes of pneumonia were noted in 239 patients (28.3%). Of these patients, 186 (78.2%) had one episode, 37 (15.5%) had two episodes, ten (4.2%) had three episodes, and five (2.1%) had four episodes. The overall frequency of pneumonia in this population was 0.87 episodes per 1,000 patient days at risk.

Patients younger than 5 years had a higher incidence (35%) of pneumonia than did those 5 years or older (20%) ($P < .001$). No correlation was noted between the WBC count and/or the presence of mediastinal mass at the time of diagnosis of ALL and the incidence of pneumonia.

Episodes were most common during February and March (1.25 per 1,000 patient days) and at their lowest frequency during July and August (0.65/1,000 patient days). The incidence of pneumonia varied between participating institutions, the range being 0.27 to 1.78 episodes per 1,000 patient days.

Cause of Pneumonia

A specific cause for individual episodes was assigned only if pathogenic organisms were identified in cultures of blood, sputum, or lung tissue, or in histologic sections of lung obtained premortem or postmortem. Cultures of material from upper airway sites, ie, throat or nasopharynx, were not considered adequate for this purpose. The designation of "interstitial" pneumonia was reserved for those episodes in which examination of a lung biopsy specimen showed no specific causative organisms, but did show an interstitial, inflammatory process accompanied by varying degrees of tissue necrosis. Episodes of pneumonia not meeting any of these criteria were classified as of "undetermined" origin.

Table 1 gives the results of these studies. Eighty percent of all episodes were classified as being of undetermined origin. Bacterial and *P carinii* pneumonias predominated in episodes with documented cause. Cases of bacterial or fungal pneumonia were seen at nine of 20 participating institutions, whereas 12 centers reported cases of *P carinii* pneumonia. The distribution of cases with documented cause appeared random. Mixed infections were noted in five cases (Table 1), including two of the 22 cases of *P carinii* pneumonia.

Lung biopsies or aspirations were performed in 53 of the episodes. Thirty were open surgical biopsies and 23 were needle biopsies. A definite causative organism was identified from 20 (66%) of the open-biopsy specimens and from seven (30%) of the specimens obtained by closed proce-

dures. In an additional eight open-biopsy specimens (27%), a histologic diagnosis of "interstitial" pneumonia was made.

Cultures of blood were obtained in conjunction with 174 of the 310 episodes. Pathogens were recovered from the blood in 14 (9%) of such episodes. *Staphylococcus aureus* (five episodes), *Escherichia coli* (four episodes) and *Streptococcus pneumoniae* (three episodes) were the most commonly identified organisms.

Time of Onset of Pneumonia

Figure 2 illustrates the relationship of time of onset of pneumonia to diagnosis of ALL and start of antileukemic therapy. An increased incidence of pneumonia was noted at or within 20 days of diagnosis of ALL. However, the peak incidence of episodes was clearly in the time period of 40 to 80 days after diagnosis. Seventy percent of all first episodes and 63% of all episodes occurred within the first 100 days of therapy. No major interinstitutional variation in this pattern was noted. No relationship was noted between time of onset of pneumonia and age of the patient or the type of CNS intensification regimen used.

Proven bacterial and/or fungal pneumonias occurred primarily in the first 20 days, whereas the majority of cases of *P carinii* pneumonia were noted in the period of 40 to 120 days following initiation of therapy for ALL (Fig 3). No cases of *P carinii* or interstitial pneumonia occurred in the first 40 days. These differences in the relative time distribution of the two etiologic categories are highly significant ($P = .0001$, χ^2 test for a 2×2 contingency table).

Presentation and Pneumonia Episodes

Temperature higher than 38 °C (82% of all episodes) and cough (78%) were the most common symptoms associated with pneumonia in this patient population. Tachypnea (42%) and cyanosis (10%) were less commonly noted. Only 11% of all episodes were accompanied by a recent history of upper respiratory tract infection or pulmonary disease in immediate family members. No relationship be-

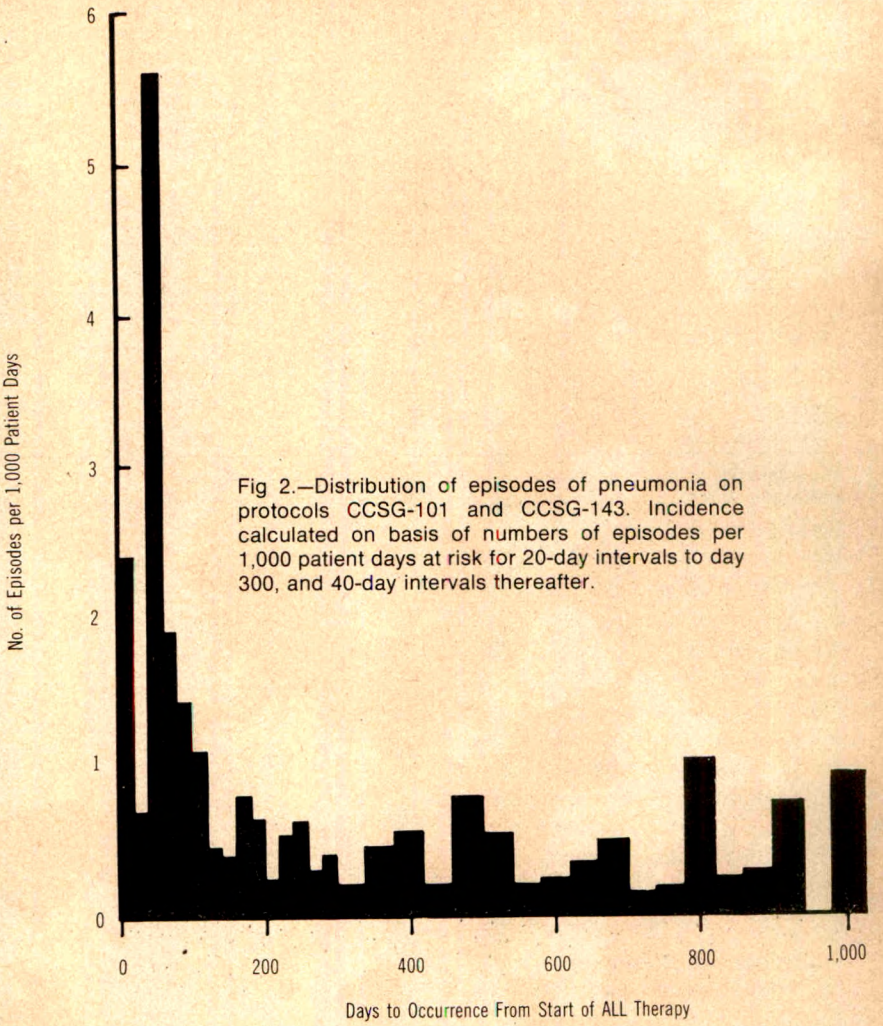

Fig 2.—Distribution of episodes of pneumonia on protocols CCSG-101 and CCSG-143. Incidence calculated on basis of numbers of episodes per 1,000 patient days at risk for 20-day intervals to day 300, and 40-day intervals thereafter.

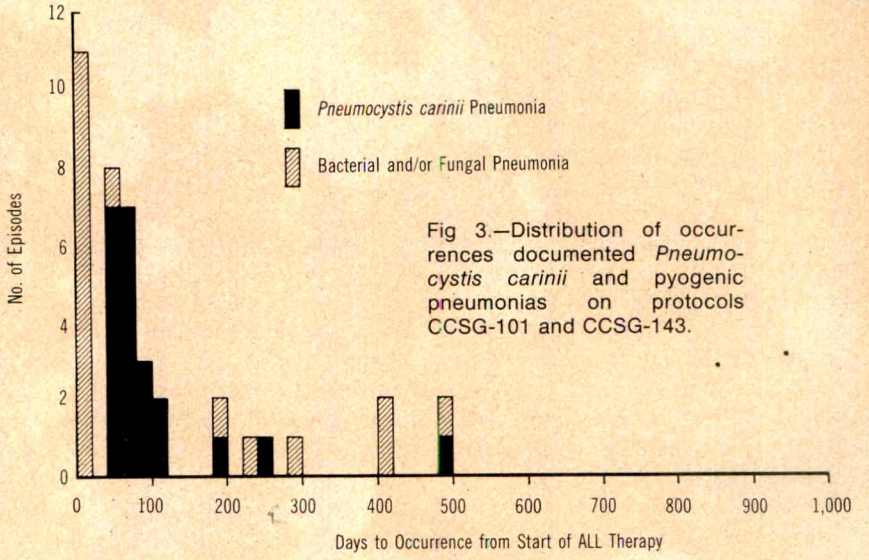

Fig 3.—Distribution of occurrences documented *Pneumocystis carinii* and pyogenic pneumonias on protocols CCSG-101 and CCSG-143.

Table 2.—Intensification Regimen vs Cause and Incidence of Pneumonia*

	Regimen				
	1: Extended Field, Craniospinal Radiation	2: Craniospinal Radiation	3: Cranial Radiation, Intrathecal Methotrexate	4: ≥18 mo of Age At Diagnosis, Intrathecal Methotrexate	4: <18 mo of Age at Diagnosis, Intrathecal Methotrexate
Cause					
Bacterial and/or fungal	3	1	2	1	0
Viral	5	1	1	0	1
Pneumocystis carinii	2	2	8	7	3
"Interstitial"	1	1	2	2	2
Undetermined	37	51	61	53	17
Total episodes (N = 264)	**48**	**56**	**74**	**63**	**23**
Total episodes per 1,000 days at risk	0.72	0.61	0.79	0.80	1.37

*Only episodes on protocols CCSG-101 and CCSG-143 occurring during intensification and maintenance phases (N = 264) are included in this table. The 46 episodes noted during the induction phase are excluded since they could not be affected by the subsequent intensification program.

tween these findings and the cause of the episodes were noted, with the exception of an increased frequency of tachypnea (80%) and cyanosis (45%) in *P carinii* pneumonia. *Pneumocystis carinii* and interstitial pneumonias were more commonly associated with diffuse pulmonary infiltrates on chest roentgenogram (79%), whereas bacterial and/or fungal pneumonias and pneumonias of undetermined cause demonstrated predominantly patchy infiltrates (78%).

Relationship of Pneumonia to Intensification Regimen

Table 2 gives the relationship of the cause of pneumonia occurring *only* during intensification and maintenance phases of therapy to the type of intensification regimen used for these patients. *Pneumocystis carinii* and interstitial pneumonias occurred at a significantly higher frequency in patients receiving intensification regimens 3 and 4 than in those patients receiving regimens 1 and 2 ($P < .01$, life table comparison by summary χ^2 statistic).[21] Children younger than 18 months of age, all of whom had received regimen 4, were excluded from this analysis. The time distribution of cases of *P carinii* pneumonia was similar in regimens 1 and 2 vs regimens 3 and 4 (Fig 4).

No significant differences in *overall* incidence of pneumonia were noted between the four intensification groups. However, patients younger than 18 months of age at the time of diagnosis of ALL, all of whom received IT methotrexate only, had a higher incidence than did older patients.

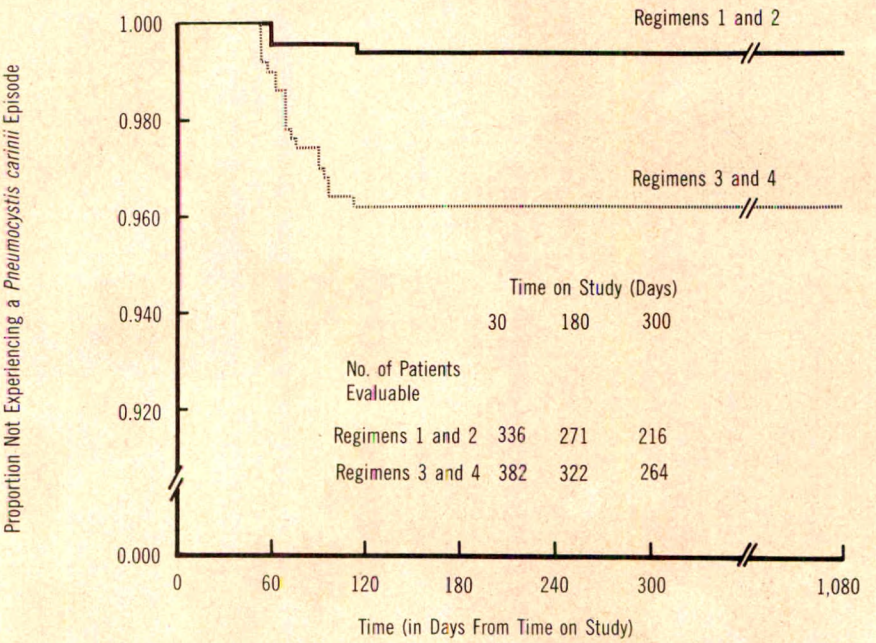

Fig 4.—Relationship of occurrence of proved *Pneumocystis carinii* pneumonia and intensification regimen. Patients were entered in this analysis after competing induction therapy and obtaining a bone-marrow remission.

Relationship of Peripheral Blood Cell Counts at Onset and Cause of Pneumonia

Absolute granulocyte counts less than 500/cu mm were associated with the onset of 49% of all pneumonias that occurred during induction therapy of ALL, whereas only 8% and 20% of all pneumonias in the intensification and maintenance phases, respectively, were associated with this level of granulocytopenia. Nine of 18 episodes of documented bacterial and/or fungal pneumonia occurred in the presence of counts of less than 500/cu mm, whereas only three of 30 episodes of *P carinii* or interstitial pneumonia and 35 of 248 pneumonias of undetermined cause were noted at this level ($P < .0001$) (Table 3). No relationship was noted between the timing or cause of pneumonia and the absolute lymphocyte count, hemoglobin level, or platelet count.

Table 3.—Relationship of Cause of Pneumonitis to Absolute Granulocyte Count at Onset*

Cause, No. of Cases	Absolute Granulocyte Count, cu mm				
	<100	100-499	599-749	750-999	>1,000
Bacterial and/or fungal, 18	6	4	0	1	7
Viral, 8	0	1	0	0	7
Pneumocystis carinii, 22	1	2	1	0	18
Interstitial, 8	1	0	0	0	7
Undetermined, 248	16	19	8	15	190

*Six episodes not evaluable.

Table 4.—Outcome of Episodes (N = 299)*

Cause, No. of Cases	Asymptomatic Within 1 wk	Asymptomatic Within 3 wk	Asymptomatic Within 6 wk	'Chronic' Pulmonary Disease	Died
Bacterial and/or fungal, 18	1	6	4	1	6
Viral, 8	2	2	1	1	2
Pneumocystis carinii, 22	1	14	2	0	5
"Interstitial," 8	4	3	0	0	1
Undetermined, 243	112	92	25	10	4
Total (% of Cases)	**120** (40.6)	**117** (38.6)	**32** (10.8)	**12** (4.0)	**18** (6.0)

*Outcomes of 11 episodes not available.

Course and Outcome of Pneumonia

Eighteen (6.1%) of the 299 episodes in which the outcome was known resulted in death; thus, the overall mortality for pneumonia in this population of 844 patients with ALL was 2.1%, or 0.05 deaths per 1,000 patient days at risk. Nonfatal results were classified by the period of time from diagnosis of pneumonia until complete resolution of symptoms and roentgenographic changes. Patients with roentgenographic infiltrates persisting for more than six weeks accompanied by continued symptoms of pulmonary involvement, ie, cough, fever, or tachypnea, were classified as having chronic disease.

Table 4 indicates the relationship of outcome to cause of the episodes. Approximately 80% of all episodes resolved within three weeks of diagnosis. As expected, mortality was greater for episodes of documented bacterial and/or fungal (33%) and *P carinii* pneumonia (23%) than for those of undetermined cause (2%). Mortality for patients with tachypnea and cyanosis at the time of onset was 40%, but prognosis was not influenced by other signs and symptoms. A higher mortality was noted for episodes occurring in the induction phase of antileukemic therapy (5/42, 12%) than for those occurring in the intensification (8/112, 7%), or maintenance phases (5/155, 3%).

Of the 292 episodes that could be evaluated, seven of 48 (14.5%) with absolute granulocyte counts less than 500/cu mm at time of onset of pneumonia resulted in death, whereas only 11/244 (4.5%) of episodes with counts greater than 500/cu mm ended in death, ($P = .02$, two-sided test of proportions). No relationship between hemoglobin level and platelet count at onset of episodes of pneumonia and outcome of these episodes was detected.

COMMENT

Retrospective studies of large populations of patients with acute leukemia have stressed the relatively low rate of infectious complications in children with ALL compared to adults and to patients with acute nonlymphocytic leukemia.[1,3,4] The present study clearly indicates that pneumonia is a relatively frequent cause of morbidity and, occasionally, mortality during the therapy of childhood ALL. Furthermore, the incidence of pneumonia seen in this pediatric population (0.87 episodes per 1,000 days at risk) is appreciably higher than the 0.1 episodes per 1,000 days at risk reported for all children younger than 5 years of age.[22] Specific data for children 5 years of age and older are not available, but the incidence of pneumonia in this population is estimated to be even lower than that for the younger children.[22,23]

In contrast to previous studies of this phenomenon during the therapy of acute leukemia, patients in the present study were followed up only during their initial remission induction and maintenance therapy courses. Our data, therefore, do not reflect the anticipated increased incidence of infections, including pneumonia, during periods of bone-marrow relapse. The increased incidence of pneumonia observed during early induction therapy (days 0 to 20) is consistent with that from reports in the literature.[1,2] However, the dramatic rise in frequency of pneumonia between days 40 and 80 after initiation of antileukemic therapy reported in this study has not been previously described (Fig 4).

No etiologic agent could be identified in the majority of episodes experienced in this series of patients. Documentation of the cause of episodes often required repeated cultures of blood and open-lung biopsy, particularly for interstitial pneumonias.[24] When a lung biopsy specimen was obtained, a causative organism was identified in 50% of all specimens, a recovery rate that is superior to that reported by Iacuone et al.[7]

Eleven of the 18 bacterial infections occurred during the first 20 days of induction therapy and were associated with severe granulocytopenia.[1,25] In contrast to adults with leukemia,[1,2,7] Gram-positive bacterial pathogens predominated and fungal pneumonia was a rare event. On the other hand, no episode of *P carinii* or interstitial pneumonia occurred before the 40th day of antileukemic therapy, and 25 of the 30 episodes occurred between the 40th and 120th days. These results are similar to those recently reported by

Ruebush et al[26] and Iacuone et al.[7]

The cause of this remarkable increase in incidence of *P carinii* pneumonia at this point in the therapy of ALL, particularly in patients receiving IT methotrexate for CNS prophylaxis (regimens 3 and 4), cannot be clarified in the present retrospective study. In contrast to the report of Iacuone et al,[7] lymphopenia did not play a role in this phenomenon in our patients.[7] Chemotherapeutic agents, particularly methotrexate and corticosteroids, have been shown to cause abnormalities to tissue macrophage function, but further prospective evaluations in children with ALL are necessary to determine if such a mechanism is related to the present findings.[27,28]

The results of this study should encourage the clinician to be aware of the frequency of pneumonia during the therapy of ALL, particularly during the first 120 days of treatment. The high incidence of pneumonias of unknown cause suggest that more vigorous attempts at diagnosis are needed to direct specific therapeutic intervention, particularly for those patients with diffuse interstitial infiltrative findings on chest roentgenogram. Furthermore, the results of this study support a role for early prophylactic therapy for *P carinii* pneumonia as part of therapeutic regimens for ALL.[29]

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Leslie Robison and Carolyn Level assisted in collection and retrieval of data for this study, and Ann McBride prepared the manuscript.

Nonproprietary Name and Trademark of Drug

Vincristine sulfate—*Oncovin*.

References

1. Levine AS, Schimpff SC, Graw RG Jr, et al: Hematologic malignancies and other marrow failure states: Progress in the management of complicating infections. *Semin Hematol* 11:141-205, 1974.

2. Bodey GP, Powell RD Jr, Hersh EM: Pulmonary complications of acute leukemia. *Cancer* 19:781-793, 1966.

3. Hughes WT, Feldman S, Cox F: Infectious diseases in children with cancer. *Pediatr Clin North Am* 21:583-615, 1974.

4. Hughes WT, Smith DR: Infection during induction of remission in acute lymphocytic leukemia. *Cancer* 31:1008-1014, 1973.

5. Hersh EM, Bodey GP, Nies BA, et al: Causes of death in acute leukemia. *JAMA* 193:105-109, 1965.

6. Simone JV, Holland E, Johnson W: Fatalities during remission of childhood leukemia. *Blood* 39:759-770, 1972.

7. Iacuone JJ, Wong KY, Bove KE, et al: Acute respiratory illness in children with acute lymphoblastic leukemia. *J Pediatr* 90:915-919, 1977.

8. Rubin P, Casarett GW: *Clinical Radiation Pathology*. Philadelphia, WB Saunders Co, 1968, vol 1, pp 423-470.

9. Wohl MEB, Griscom NT, Traggis DG: Effects of therapeutic irradiation delivered in early childhood upon subsequent lung function. *Pediatrics* 55:507-516, 1975.

10. Smith JC: Radiation pneumonitis. *Am Rev Respir Dis* 87:647-655, 1963.

11. Boushy SF, Helgason AH, North LB: The effect of radiation on the lung and bronchial tree. *Am J Roentgenol* 108:284-292, 1960.

12. Weir GJ, Michaelson SM: *Pulmonary Radiation Reactions*. Springfield, Ill, Charles C Thomas Publishers, 1971.

13. Whitfield AGW, Bond WH, Kunkler PB: Radiation damage to thoracic tissues. *Thorax* 18:371-380, 1963.

14. Clarysse AM, Cathey WJ, Cartwright GE, et al: Pulmonary disease complicating intermittent therapy with methotrexate. *JAMA* 209:1861-1864, 1969.

15. Robbins KM, Gribetz E, Strauss L, et al: Pneumonitis in acute lymphatic leukemia during methotrexate therapy. *J Pediatr* 82:84-88, 1963.

16. Whitcomb ME, Schwartz MI, Tormey DC: Methotrexate pneumonitis: Case report and review of the literature. *Thorax* 27:636-639, 1972.

17. Everts CS, Westcott JL, Bragg DG: Methotrexate therapy and pulmonary disease. *Radiology* 107:539-543, 1973.

18. Bhat KSS, Anderson KR, Stewart RDH: Lung disease associated with methotrexate therapy. *Aust NZ J Med* 4:277-280, 1974.

19. Lisbona A, Schwartz J, Lachance C, et al: Methotrexate-induced pulmonary disease. *J Canad Assoc Radiol* 24:215-220, 1973.

20. Iyer R, Ravindramath Y, Kulkaini R, et al: Bilateral interstitial pneumonia in acute lymphoblastic leukemia. *Am J Hematol* 1:225-235, 1976.

21. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. *Br J Cancer* 35:1-39, 1977.

22. Wilder CS: Acute respiratory illnesses reported to the US National Health Survey during 1957-1962. *Am Rev Respir Dis* 88:14-21, 1963.

23. Glezen WP, Loda FA, Clyde WA, et al: Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J Pediatr* 78:397-406, 1971.

24. Wolff LJ, Bartlett MS, Baehner RL, et al: The causes of interstitial pneumonitis in immunocompromised children: An aggressive systematic approach to diagnosis. *Pediatrics* 60:41-45, 1977.

25. Bodey GP, Buckley M, Sathe YS, et al: Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 64:328-340, 1966.

26. Ruebush TK, Weinstein RA, Baehner RL, et al: An outbreak of pneumocystis pneumonia in children with acute lymphocytic leukemia. *Am J Dis Child* 132:143-148, 1978.

27. Newhouse M, Sanchis J, Bieronstock J: Lung defense mechanisms. *N Engl J Med* 295:1045-1052, 1976.

28. Sieger L: Pulmonary alveolar macrophages in pre- and post-natal rabbits. *J Reticuloendothel Soc* 23:389-395, 1978.

29. Hughes WT, Kuhn RN, Chaudhary MD, et al: Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 297:1419-1426, 1977.

Prevention of Pneumocystis Pneumonia

Use of Continuous Sulfamethoxazole-Trimethoprim Therapy

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• Owing to a 15% attack rate of *Pneumocystis carinii* pneumonitis (PCP) among the leukemic population at Riley Hospital, Indianapolis, a two-year study using continuous low-dosage sulfamethoxazole-trimethoprim to prevent PCP was started in January 1977. A total of 229 pediatric cancer patients considered at high risk for getting PCP received prophylaxis, while 19 additional low-risk cancer patients did not receive sulfamethoxazole-trimethoprim. None of these 248 patients contracted PCP. However, five cases of PCP did occur among ten additional high-risk patients who failed to receive this preparation for a variety of reasons. Complications of the continuous prophylaxis program included neutropenia, rash, and gastrointestinal complaints. This study confirms that continuous, low-dosage sulfamethoxazole-trimethoprim prophylaxis is effective in preventing PCP in susceptible immunosuppressed patients but is ineffective in eradicating the organism from the population at risk.

(*Am J Dis Child* 134:35-38, 1980)

Pneumocystis carinii, a ubiquitous protozoan organism that may reside symbiotically in the respiratory system of man and animals,[1] develops pathogenic potential in immunosuppressed patients.[2] This group includes patients with cancer undergoing chemotherapy or radiation therapy[3,4] and patients receiving immunosuppressives for a variety of disease states.[5-9] In addition, severely malnourished[10] or congenitally immunodeficient patients[11] may have a rapidly progressive and often fatal interstitial pneumonitis owing to this protozoan. Only rarely is PCP found in normal, healthy individuals.[12]

Diagnosis of *P carinii* pneumonitis (PCP) is established by identification of the organism in lung tissue obtained either by open lung biopsy[13] or by percutaneous lung aspirate.[14] The incidence of PCP differs widely among institutions but can be related to the intensity of immunosuppressive therapy.[3] Treatment of PCP with either sulfamethoxazole-trimethoprim[15-19] or pentamidine[20-22] has improved morbidity and mortality from this illness to as low as 5%.[22] Prior to effective treatment, mortality was as high as 100%.

Ideally, an effective program to prevent the development of PCP in immunosuppressed patients would reduce morbidity as well as mortality. Initially, we gave a two-week course of sulfamethoxazole-trimethoprim to susceptible leukemic patients four to six weeks after institution of therapy in an effort to prevent PCP.[23] We observed a delay in the onset of PCP, but our program failed to reduce the high attack rate among our patient population. A prophylactic program for PCP was recently reported from St Judes Hospital[24] and indicated that low-dosage continuous administration of this preparation was effective in preventing PCP in susceptible individuals. The results of this present study confirm the latter observation but point out that such a widespread prophylactic program does not eradicate the protozoan from the patients' environment and is associated with minimal side effects.

STUDY DESIGN

The prophylactic program for PCP consisted of sulfamethoxazole-trimethoprim (Bactrim) at a daily oral dosage of 20:4 mg/kg/day on a twice-a-day schedule. All children with a diagnosis of cancer were entered into the study, but only those who received chemotherapy or extensive radiation therapy from January 1977 to January 1979 were considered to be at high risk and they were the ones who received prophylaxis. Children with cancer who did not receive chemotherapy or who received only radiation therapy to localized areas of the body were considered to be at low risk and did not receive prophylaxis. The projected attack rates for the high-risk group, based on our past experience with children with acute lymphoblastic leukemia (ALL), were 15% and 17%.[3,23] The projected

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attack rate was 0% for the low-risk group.

Children with ALL began treatment with the mixture at the start of CNS prophylaxis (day 28) and continued prophylaxis for a minimum of one year. Children with acute nonlymphocytic leukemia (ANLL) and solid tumors began to receive prophylaxis at the start of therapy and prophylaxis was continued for a period six months after all cancer therapy had been stopped.

Parents and patients were informed of the purpose of the study, its potential benefits, and possible side effects; and they were asked to sign a written consent form in accordance with the policies of our institution's Human Investigations Committee before being placed in the prophylactic study. The sulfamethoxazole-trimethoprim was provided in suspension and tablet form. All patients were followed up in the hematology-oncology clinic. Blood levels of trimethoprim were not monitored for each patient, but random samples for sulfa levels supported our clinical impression that compliance was exceptionally good.

REPORT OF CASES

From January 1977 through December 1978, prophylaxis was received by 229 patients, including 110 with solid tumors, 101 with ALL, and 18 with ANLL (high-risk group receiving prophylaxis). The conditions of an additional 19 patients were diagnosed as being solid tumors, but the patients were not placed in the sulfamethoxazole-trimethoprim study because they were not considered at risk for PCP (low-risk group without prophylaxis). Another eight patients (one with ANLL, four with ALL, three with solid tumors) who died early in their courses of therapy were not entered into the prophylactic study. None of these patients had evidence of PCP at autopsy. Review of our pediatric cancer population disclosed ten patients who inadvertently failed to receive prophylactic sulfamethoxazole-trimethoprim. Because of the intensity of their therapy (three with ALL, one with ANLL, six with solid tumors), this group constituted our high-risk group that did not receive prophylaxis (Table).

There were no cases of PCP among the 229 who received Bactrim or among the 19 low-risk patients not receiving prophylaxis. However, among the ten high-risk patients who inadvertently failed to receive the preparation, five cases of PCP were encountered. Their case histories follow:

Results of *Pneumocystis carinii* Pneumonitis (PCP) Prevention Study

Group	No. of Patients*				Contracted PCP
	ALL	ANLL	Solid Tumors	Total	
Prophylaxis, high-risk	101	18	110	229	None
No prophylaxis, low-risk	0	0	19	19	None
No prophylaxis, high-risk	3	1	6	10	5†
Died too soon	4	1	3	8	None

*ALL indicates acute lymphoblastic leukemia; ANLL, acute nonlymphocytic leukemia.
†Includes three with ALL, one with ANLL, and one with a solid tumor.

Case 1.—A 3-year 5-month-old boy was referred to Riley Hospital, Indianapolis, in December 1977 with suspected leukemia. A diagnosis of null cell ALL was made by bone marrow aspiration and he was placed on the Children's Cancer Study Group protocol 141A with a 28-day induction program of vincristine sulfate, prednisone, and asparaginase, CNS prophylaxis consisting of 2,400 rads of cranial radiation, six doses of intrathecal methotrexate sodium, and daily oral mercaptopurine, followed by a maintenance regimen with monthly vincristine-prednisone pulses, daily mercaptopurine, and weekly methotrexate. Because of a low red cell glucose-6-phosphate dehydrogenase (G6PD) level at diagnosis, the patient was not given sulfamethoxazole-trimethoprim. On April 18, 1978, he was admitted with fever, tachypnea, hypoxia, and bilateral patchy interstitial infiltrates on his chest roentgenogram. Examination of the open lung biopsy specimen disclosed PCP, and he rapidly responded to a ten-day course of intramuscular (IM) pentamidine at 4 mg/kg/day. Even though repeated G6PD levels at this time still were borderline low, he was given a trial of low-dosage sulfamethoxazole-trimethoprim after recovery from PCP, and hemolysis failed to develop. He has remained well to date with prophylaxis.

To prevent recurrence of PCP, it has been our policy to begin continuous low-dosage prophylaxis on full recovery from the pneumonitis. Recurrence of PCP in two patients who did not receive such prophylaxis has recently been reported by Tebbi.[25]

Case 2.—A 5-month-old female infant referred to Riley Hospital in the autumn of 1976 for anemia (hemoglobin level, 6.0 g/dL) and leukocytosis (WBC count, 157,000/cu mm). On admission, a bone marrow aspiration revealed null cell ALL; she received a 28-day induction course consisting of vincristine, prednisone, and asparaginase. She had CNS leukemia at the end of the otherwise successful induction and received six doses of intrathecal methotrexate along with 2,000 rads of cranial radiation during the ensuing four weeks. The lymphoblasts cleared from the spinal fluid. She was one of the last patients to be placed in our previous PCP prophylactic study. She received a two-week course of either sulfamethoxazole-trimethoprim at 100:20 mg/kg/day or placebo beginning on day 28. In January 1977, we began the present prophylactic study and gave all patients still receiving therapy and all patients with newly diagnosed conditions continuous low-dosage sulfamethoxazole-trimethoprim. This patient was overlooked until the 66th day after diagnosis of ALL when she had fever, tachypnea, hypoxia, and interstitial infiltrates on her chest roentgenogram. Examination of an open lung biopsy specimen showed PCP. She was treated with IM pentamidine at 4 mg/kg/day for ten days and recovered uneventfully. When the code of the double-blind study was broken, it was discovered she had received the placebo. She subsequently received sulfamethoxazole-trimethoprim prophylaxis but sustained a bone marrow relapse in September 1977 and died in October 1977.

Case 3.—The patient, a male infant, was referred in May 1977 at 4 months of age for bilateral axillary and inguinal lymphadenopathy. The node biopsy specimen indicated histiocytosis-X and further evaluation showed radiolucencies in the right anterior maxilla and the left mandibular alveolar ridge. He was placed on a regimen of daily oral prednisone and weekly intravenous (IV) vinblastine sulfate, with subsequent great decrease in the lymphadenopathy. By oversight, he was not placed in the PCP prophylactic study. In July 1977, he had tachypnea, hypoxia, and fever. An open lung biopsy specimen showed PCP, and his condition was treated with sulfamethoxazole-trimethoprim at 100:20 mg/kg/day orally for 14 days while his prednisone dosage was tapered. The infection quickly cleared, but he had a diffuse, fine, erythematous maculopapular rash while receiving Bactrim. The rash desquamated and then cleared after discontinuance of prophylaxis with the mixture. The open

lung biopsy specimen also showed pulmonary involvement with histiocytosis-X. Based on this observation, his chemotherapy was subsequently changed to a more aggressive program consisting of vinblastine, prednisone, cyclophosphamide (Cytoxan) and methotrexate. At the present time, he has no evidence of active histiocytosis-X. He has not been given prophylaxis with sulfamethoxazole-trimethoprim again because of the rash he had while receiving the antibiotic.

CASE 4.—This female patient was referred in March 1977 at age 3 years and 2 months for evaluation of fever, pallor, and petechiae. Bone marrow examination revealed acute monocytic leukemia, and she was given an induction regimen consisting of daunorubicin hydrochloride, vincristine, prednisone, azacitidine, and cytarabine (cytosine arabinoside). She achieved a marrow remission, but her induction phase was complicated by measles. She inadvertently failed to receive sulfamethoxazole-trimethoprim prophylaxis. In June 1977, she had fever, tachypnea, hypoxia, and diffuse interstitial infiltrates. Her open lung biopsy specimen indicated PCP that rapidly responded to pentamidine at 4 mg/kg/day for ten days. She was subsequently given sulfamethoxazole-trimethoprim continuous prophylaxis and remains in remission at the present time while receiving monthly courses of vincristine, azacitidine, cytarabine, and oral thioguanine.

CASE 5.—A 3-year 2-month-old girl was referred to Riley Hospital on Sept 19, 1978 for fever, epistaxis, and ecchymoses. A bone marrow aspiration showed null cell ALL and she was placed on a 28-day induction program consisting of vincristine, prednisone, and asparaginase and six weekly doses of intrathecal methotrexate. Central nervous system prophylaxis was continued at 3-month intervals with intrathecal methotrexate (in lieu of cranial radiation). Maintenance therapy consisted of daily oral mercaptopurine and weekly oral methotrexate. Because she did not receive cranial irradiation or monthly vincristine-prednisone pulses, it was decided not to give her sulfamethoxazole-trimethoprim prophylaxis. On Nov 4, 1978, she had cough and fever, and a chest roentgenogram indicated a right middle lobe infiltrate. She was given a ten-day course of oral amoxicillin trihydrate, but she failed to respond. Thus, she was hospitalized, treated with IV ampicillin sodium, and given low-dosage sulfamethoxazole-trimethoprim (20:4 mg/kg/day) prophylaxis. Two days later, she was discharged on a regimen of oral amoxicillin and sulfamethoxazole-trimethoprim. However, four days thereafter, she again had fever and mild respiratory distress and was readmitted to the hospital on Nov 20, 1978. The sulfamethoxazole-trimethoprim and amoxicillin therapies were discontinued, and she was observed. She had tachypnea, hypoxia, and rapidly progressive interstitial infiltrates. Study of an open lung biopsy specimen on Nov 22, 1978 revealed PCP. She was again given Bactrim at a dosage of 100:20 mg/kg/day and experienced extremely rapid improvement. After a 14-day course of this mixture, she was given its low prophylactic dosage, which she continues to take at present.

Patient 5 is also of special interest because her case history demonstrates that low-dosage prophylaxis with sulfamethoxazole-trimethoprim (20:4 mg/kg/day) may not cure an already clinically infected host, whereas a higher dosage of this preparation (100:20 mg/kg/day) usually will.

COMPLICATIONS OF PROPHYLAXIS

Rash

Among the 229 patients given sulfamethoxazole-trimethoprim prophylaxis, five had rashes owing to this preparation, and three others had a rash possibly owing to the use of this mixture, for an incidence of 3.5%. One patient had hives directly attributable to Bactrim because of its rapid reoccurrence on rechallenge with this mixture. Another child had Stevens-Johnson syndrome owing to this preparation and recovered after withdrawal of the drug and a short course of prednisone at 2 mg/kg/day. The other patients with rash had fine, diffuse maculopapular erythematous lesions generally associated with mild pruritis. In two of these patients, the rash was associated with mild pruritis. In two of these patients, the rash was associated with eosinophilia.

Gastrointestinal (GI) Effects

Three patients were suspected of having nausea and vomiting in association with sulfamethoxazole-trimethoprim usage (incidence, 1.3%). When treatment with the drug was discontinued, the nausea and vomiting ceased. However, none of the patients experienced GI discomfort on rechallenge with this combination at a later date.

Neutropenia

Because of concomitant chemotherapy or radiation therapy, neutropenia induced by sulfamethoxazole-trimethoprim usage was difficult to prove in most cases. However, neutropenia was well documented to be due to this preparation in five patients, and the drug was suspected to be possibly contributing to neutropenia in six other patients (incidence, 4.8%). All well-documented cases showed resolution of the neutropenia when prophylaxis with this mixture was discontinued even though chemotherapy was continued. A typical case history follows:

A 6-year 10-month-old boy was referred in January 1977 for evaluation of a left chest wall mass. A biopsy specimen of the mass showed Ewing's sarcoma. He was initially treated with vincristine, cyclophosphamide, and doxorubicin hydrochloride (Adriamycin) to reduce the size of the mass. Irradiation therapy was begun in March 1977 to further reduce the mass prior to complete surgical resection carried out in May 1977. Since then, he has continued to receive multiagent chemotherapy, with no evidence of recurrence. Sulfamethoxazole-trimethoprim prophylaxis was started at the time of diagnosis. During his maintenance cycles of weekly IV cyclophosphamide and vincristine, he had many delays and reductions in dosage of chemotherapy owing to neutropenia. On June 6, 1978, sulfamethoxazole-trimethoprim prophylaxis was discontinued on the suspicion that it was contributing to his neutropenia, but the chemotherapy was continued. The next week, his absolute granulocyte count increased from 650 to 3,400/μL, and since then, he has been able to tolerate full-dosage chemotherapy with no delays.

COMMENT

For several years, our institution has experienced an unusually high (15% ± 7%) attack rate of pneumocystis pneumonitis among its immunosuppressed leukemic population.[3,23] Similar epidemics had previously been encountered in the same population at other institutions.[26,27] In 1975, an investigation at Riley Hospital by the Center for Disease Control,[3] Atlanta, suggested that transmission of pneumocystis was occurring within the hospital environment since the hospital staff with close contact with the susceptible patients had a higher

prevalence of elevated antibody titers than other staff members. In addition to the leukemic population, a systematic diagnostic approach to cases of interstitial pneumonitis in patients with solid tumors also frequently identified PCP.[13]

In an attempt to reduce the attack rate among the entire cancer population, children at risk for PCP were treated with a two-week course of sulfamethoxazole-trimethoprim at a dosage of 100 and 20 mg/kg/day of sulfamethoxazole and trimethoprim, respectively. The results of the institutional study showed that the prophylaxis did not decrease the attack rate but only delayed the occurrence of the pneumonitis by about four months.[23]

Because of the failure of the two-week, full-dosage course of this mixture to prevent PCP, the present study was started in January 1977. Hughes et al[24] had shown that low-dosage (20:4 mg/kg/day) sulfamethoxazole-trimethoprim prophylaxis continued throughout the period of cancer therapy totally prevented PCP. Our study confirmed this prior observation since none of the 229 patients who received continuous prophylaxis had PCP. Of importance were the five cases of PCP developing among the ten patients who were at risk but failed to receive this preparation. This observation demonstrates the continued presence of the protozoan in the environment and its failure to be eradicated by the prophylactic program. This study does not prove that the drug did or did not eradicate the organism from treated patients. On termination of prophylaxis with the drug, new organisms could have been acquired from exogenous sources. This study also points out the extreme effectiveness of sulfamethoxazole-trimethoprim in prevention of PCP. As noted in patient 5, successful treatment of PCP requires the higher dosage since the protozoan remained in the lung of the patient receiving the lower dosage of this mixture for a full week. Side effects from the preparation encompassed a variety of rashes, neutropenia, and occasional GI complaints. However, these side effects must be weighed against its effectiveness in prevention of PCP in these high-risk patients.

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Nonproprietary Names and Trademarks of Drugs

Amoxicillin trihydrate—*Amoxil, Larotid, Robamox Robicaps, Sumox, Trimox.*
Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*
Asparaginase—*Crasnitin, Elspar.*
Daunorubicin hydrochloride—*Cerubidine.*
Sulfamethoxazole-trimethoprim—*Bactrim.*
Vinblastine sulfate—*Velban.*
Vincristine sulfate—*Oncovin.*

References

1. Pifer LL, Hughes WT, Stagno S, et al: *Pneumocystis carinii* infection: Evidence for high prevalence in normal and immunosuppressed children. *Pediatrics* 61:35-41, 1978.
2. *Pneumocystis carinii* pneumonitis, editorial. *Lancet* 2:1023-1024, 1975.
3. Ruebush TK II, Weinstein RA, Baehner RL, et al: An outbreak of pneumocystis pneumonia in children with acute lymphocytic leukemia. *Am J Dis Child* 132:143-148, 1978.
4. Wolff LJ, Bartlett MS, Baehner RL, et al: The causes of interstitial pneumonitis in immunocompromised children: An aggressive systematic approach to diagnosis. *Pediatrics* 60:41-45, 1977.
5. Walzer PD, Perl DP, Krogstad DJ, et al: *Pneumocystis carinii* pneumonia in the United States. *Ann Intern Med* 80:83-93, 1974.
6. Endo F, Matsukwa M, Maeda T, et al: Diagnosis and treatment of *Pneumocystis carinii* pneumonia. *Arch Dis Child* 53:87-88, 1978.
7. Briggs WA, Merrill JP, O'Brien T, et al: Severe pneumonia in renal transplant patients. *Ann Intern Med* 75:887-894, 1971.
8. Solberg CO, Meuivisson HJ, Needham RN, et al: Infectious complications in bone marrow transplant patients. *Br Med J* 1:18-23, 1971.
9. Bourgault AM, Van Scoy RE, Brewer NS, et al: Trimethoprim with sulfamethoxazole for treatment of infection with *Pneumocystis carinii* in renal insufficiency. *Chest* 74:91-92, 1978.
10. Redman JC: Vietnamese malnourished infants. *JAMA* 231:1190-1191, 1975.
11. Walzer PD, Schultz MG, Western KA: *Pneumocystis carinii* pneumonia and primary immune deficiency syndromes. *J Pediatr* 79:748-754, 1971.
12. Rao M, Steiner P, Victoria MS, et al: *Pneumocystis carinii* pneumonia: Occurrence in a healthy American infant. *JAMA* 238:2301, 1977.
13. Ballantine TVN, Grosfeld JL, Knapek RM, et al: Interstitial pneumonitis in the immunologically suppressed child: An urgent surgical condition. *J Pediatr Surg* 12:501-508, 1977.
14. Chaudhary S, Hughes WT, Feldman S, et al: Percutaneous transthoracic needle aspiration of the lung: Diagnosing *Pneumocystis carinii* pneumonitis. *Am J Dis Child* 131:902-907, 1977.
15. McLennan G, Antic R, Seymour AE, et al: *Pneumocystis carinii* pneumonitis successfully treated with trimethoprim-sulfamethoxazole. *Aust NZ J Med* 7:299-301, 1977.
16. Larter WE, John TJ, Sieber OF, et al: Trimethoprim-sulfamethoxazole treatment of *Pneumocystis carinii* pneumonitis. *J Pediatr* 92:826-828, 1978.
17. Hughes WT: Treatment of *Pneumocystis carinii* pneumonitis. *N Engl J Med* 295:726-727, 1976.
18. Lipson A, Marshall WC, Hayward AR: Treatment of *Pneumocystis carinii* pneumonia in children. *Arch Dis Child* 52:314-319, 1977.
19. Lau WK, Young LS: Trimethoprim sulfamethoxazole treatment of *Pneumocystis carinii* pneumonia in adults. *N Engl J Med* 295:716-718, 1976.
20. Hughes WT, Feldman S, Chaudhary SC, et al: Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of *Pneumocystis carinii* pneumonia. *J Pediatr* 92:285-291, 1978.
21. Kluge RM, Spaulding DM, Spain AJ: Combination of pentamidine and trimethoprim-sulfamethoxazole in the therapy of *Pneumocystis carinii* pneumonia in rats. *Antimicrob Agents Chemother* 13:975-978, 1978.
22. Wolff LJ, Baehner RL, Siegel S, et al: The treatment of *Pneumocystis carinii* pneumonitis (PCP) comparing trimethoprim sulfamethoxazole (TMP-SMZ) and pentamidine (PNT), abstracted. *Pediatr Res*, to be published.
23. Wolff LJ, Baehner RL: Delayed development of pneumocystis pneumonia following administration of short-term high-dose trimetho prim-sulfamethoxazole. *Am J Dis Child* 132:525-526, 1978.
24. Hughes WT, Kuhn S, Chaudhary S, et al: Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 297:1419-1426, 1977.
25. Tebbi K: Recurrence of *Pneumocystis carinii* pneumonia in patients with acute lymphoblastic leukemia, abstracted. *Proc Am Assoc Cancer Res* 20:C21, 1979.
26. Perera DR, Western KA, Johnson HD, et al: *Pneumocystis carinii* pneumonia in a hospital for children. *JAMA* 214:1074-1078, 1970.
27. Singer C, Armstrong D, Rosen PP, at al: *Pneumocystis carinii* pneumonia: A cluster of 11 cases. *Ann Intern Med* 82:772-777, 1975.

Theophylline Toxicity in Term Infants

F. Estelle R. Simons, MD; Frank R. Friesen, MD; Keith J. Simons, PhD

• The pharmacokinetics of theophylline were studied in 1-month-old term infants who received accidental overdoses of theophylline during treatment for bronchiolitis. Both infants survived without neurologic sequelae. Elimination half-life values of 14.5 and 15.2 hours, respectively, were shorter than reported in premature infants but longer than in infants aged 3 months or older. Caffeine appeared in the sera of both patients, who had not received it in any form. In term infants, elimination of theophylline may occur by *N*-methylation in contrast to older patients in whom the drug is chiefly eliminated by demethylation and oxidation. Theophylline has not been proved effective for the treatment of bronchiolitis. It should be used with caution for wheezing in very young infants until its pharmacokinetics have been studied further in nontoxic, full-term infants younger than age 3 months.

(*Am J Dis Child* 134:39-41, 1980)

The pharmacokinetics of theophylline in term infants have not been reported to date, to our knowledge. We studied the pharmacokinetics of the drug in term infants aged 4 and 5 weeks who were referred to us after accidental administrations of toxic doses of theophylline by the intravenous (IV) route for treatment of bronchiolitis.

REPORT OF CASES

CASE 1.—A 5-week-old, 3.7-kg infant who was delivered at term was hospitalized because of wheezing, coughing, cyanosis, and respiratory distress. An IV loading dose of 6.25 mg/kg of aminophylline was administered and was followed by a continuous infusion of 15 mg/kg/24 hr. Inadvertently, 15 mg/hr was infused over nine hours, at which time jitteriness and tachycardia were noted. The serum theophylline concentrations are shown in Fig 1. Levels of glucose and protein in the CSF and a cell count of the CSF were normal, as were blood glucose and serum electrolyte levels and the results of liver function tests. The serum albumin concentration was 4.3 g/dL.

The respiratory rate increased despite diminished respiratory distress and the disappearance of wheezing. During the next 24 hours, sinus tachycardia (heart rate, 182 to 220 beats per minute) was noted. The infant vomited, retched, and passed ten loose stools from which no pathogens were cultured. Wakefulness, jitteriness, intermittent clonic posturing of the legs and arms, ankle clonus, and hyperreflexia were noted during this time, but seizures did not occur. The infant recovered uneventfully.

CASE 2.—Infusion of 15 mg of aminophylline over half an hour was prescribed for a 4-week-old, 3.9-kg infant who was delivered at term and who had bronchiolitis. In error, 15 mL (750 mg) was given. A generalized tonoclonic seizure occurred 45 minutes later. On admission to the Children's Centre Hospital, Winnipeg, Manitoba, Canada, six hours after the overdose, the baby was hyperalert and tremulous, with unsustained ankle clonus and brisk deep tendon reflexes. There were no localized neurologic signs. Respiratory distress, diminished air entry, and cyanosis were present, but wheezing was not detectable. Retching occurred intermittently, and nasogastric tube suction yielded "coffee ground-like fluid." Sinus tachycardia (188 to 230 beats per minute) persisted for 60 hours.

The serum theophylline concentrations are shown in Fig 2. Serum values were as follows: sodium, 125 mEq/L; potassium, 2.8 mEq/L; and glucose, 370 mg/dL. The specific gravity of the urine was 1.031, and ketones and 170 mg/dL of glucose were present. The results of liver function tests were normal. The serum albumin concentration was 3.4 g/dL. The CSF cell count and protein and glucose levels were normal.

In the first 24 hours after admission, despite correction of the hyponatremia, five episodes of opisthotonic posturing and tonoclonic movements occurred. These were treated with 0.3 mg/kg of diazepam. On the EEG, spike and wave complexes were observed over the right and left frontocentral areas. Seizures increased in frequency 24 hours after the overdose and were treated with 10 mg/kg of IV phenobarbital sodium followed by 2.5 mg/kg every 12 hours and with 20 mg/kg of phenytoin sodium followed by 3 mg/kg every 12 hours. The serum concentrations of these drugs were 23 μg/mL and 21 μg/mL, respectively, and an EEG was normal 48 hours after the overdose. Chewing movements, eye blinking, nystagmus, staring, and deviation of the eyes continued for another 24 hours.

Wheezing recurred 60 hours after the overdose, but it resolved gradually. No respiratory, cardiac, or neurologic abnormalities were detected at discharge from the hospital.

ANALYTICAL METHODS

Theophylline and caffeine concentrations in the serum, CSF, and urine were measured by high-performance liquid chromatography.[1] The presence of caffeine was confirmed by mass spectrometry. Theophylline protein binding was measured by an ultrafiltration technique.[2]

DATA ANALYSIS

Log serum theophylline concentrations were plotted vs time.[3] Linear portions of the data were fitted to equation 1:

$$\ln Cp(t) = \ln Cp(o) - Kt, \qquad (1)$$

where $Cp(t)$ is the serum concentration at any time t, $Cp(o)$ is the serum concentration extrapolated to time zero, and K is the first-order elimination-rate constant. The serum half-life ($t_{1/2}$) was calculated using equation 2:

$$t_{1/2} = 0.693/K. \qquad (2)$$

Protein-binding values ($\beta\%$) were calculated using equation 3:

$$\beta\% = [(Dt - Df)/Dt] \times 100, \qquad (3)$$

where Df and Dt are the theophylline concentrations in the filtrate and retained material, respectively.

RESULTS

Plots of the log serum theophylline concentrations vs time were constructed for each infant (Fig 1 and 2). Serum theophylline concentrations one hour after the overdose were 76.5 μg/mL in patient 1 and 182 μg/mL in patient 2. In patient 1, the theophylline elimination half-life was 14.5 hours. In patient 2, it was 15.2 hours during the first 30 hours after theophylline overdose, but it decreased to 8.5 hours 40 hours after phenobarbital administration (that is, from 65 to 100 hours after the overdose).

In patient 2, serum and CSF theophylline concentrations at 24.5 hours were 73.6 μg/mL and 47.6 μg/mL, respectively, and at 45.4 hours, 38.2 μg/mL and 23.4 μg/mL, respectively. At 45.4 hours, the serum theophylline concentration in the sagittal sinus was 37.4 μg/mL. In patient 1, the theophylline protein-binding values were 66% and 62% at serum theophylline concentrations of 60.0 and 31.2 μg/mL, respectively. In patient 2, the theophylline protein-binding values

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were 53.4% and 68.7% at serum theophylline concentrations of 76 μg/mL and 10.7 μg/mL, respectively. The serum albumin concentrations were normal for patients of this age.

Although the infants were not breast-fed and did not receive caffeine in any form at any time after birth, the serum caffeine concentration in patient 1 was 2.4 μg/mL in two pooled samples that contained 60.0 and 31.2 μg/mL of theophylline. In patient 2, serum caffeine concentrations were 0.9 μg/mL one hour after the overdose and 10.8 μg/mL 42 hours after the overdose, when serum theophylline concentrations were 182 and 40 μg/mL, respectively (Fig 2). In a urine sample collected 45 hours after the theophylline was administered, 7.9 mg of theophylline and 0.25 mg of caffeine were found.

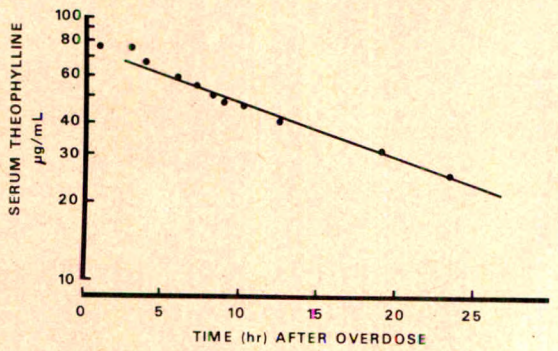

Fig 1.—Serum theophylline concentrations vs time for patient 1 at age 5 weeks. Half-life of theophylline was 14.5 hours.

COMMENT

The toxic effects of theophylline include tachycardia, other cardiac arrhythmias, hypotension, hypertension, insomnia, irritability, nervousness, tremor, convulsions, nausea, vomiting, gastrointestinal bleeding, loose stools, hyperthermia, albuminuria, and dehydration.[4] In infants, ketosis,[5] prolonged diuresis,[6] paroxysmal supraventricular tachycardia,[7] and hyperglycemia[5,8] have occurred. Both the clinical symptoms of toxicity and the lethal dose may differ according to the patient's age and ability to metabolize the drug.

Adults have had seizures and died without preceding minor symptoms (such as nausea) when serum theophylline concentrations were only 25 to 70 μg/mL. Some of these patients had abnormal hepatic function with probable low serum albumin concentrations, diminished theophylline protein binding, and excellent penetration of the drug into the CNS.[9] In an adult with hepatic failure, intractable seizures occurred when the CSF theo-

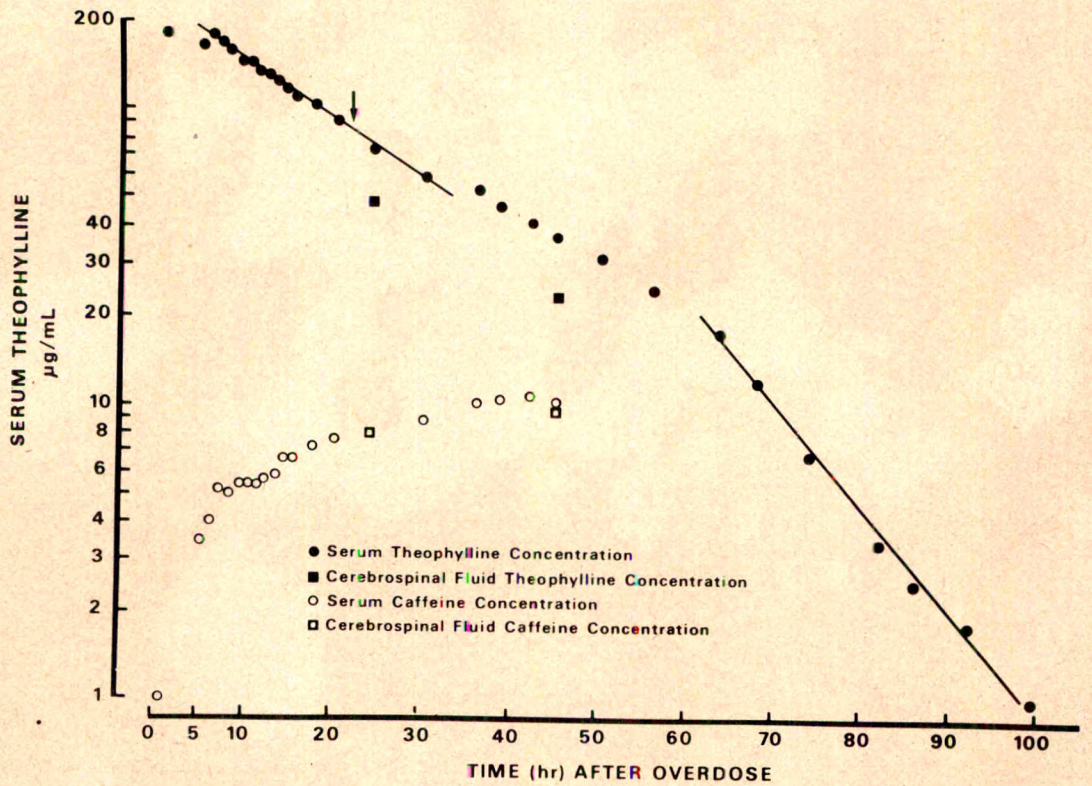

Fig 2.—Serum theophylline concentrations, CSF theophylline concentrations, and serum and CSF caffeine concentrations vs time for patient 2 at age 4 weeks. Half-life of theophylline was initially 15.2 hours, but then decreased to 8.5 hours. Arrow indicates commencement of phenobarbital therapy.

phylline concentration was 37 μg/mL compared with 40 μg/mL in the plasma.[10] Theophylline protein binding, although not measured directly, may have been diminished,[11] as serum albumin had been 2.6 g/dL.

On the other hand, in young children, survival after theophylline toxicity has been reported with a serum concentration of 141 μg/mL.[5] In our patient 2, who survived with a serum concentration of 182 μg/mL, CSF concentrations (Fig 2) were 60% to 63% of the serum concentrations, and the theophylline protein-binding value was in the normal range.[2] As serum theophylline concentrations decreased from 80 to 40 μg/mL, the seizures became more frequent despite additional treatment with anticonvulsant medication. This suggests that the lowered seizure threshold in the CNS of young infants may be associated with a critical range of theophylline concentrations above and below which seizures do not occur.

In adults with theophylline poisoning, serum concentrations have been lowered rapidly by hemodialysis using a resin[10] or charcoal[12] filter, but not all treated patients have survived.[10] In the infants described here, hemodialysis and exchange transfusions were not performed because serious signs of toxicity such as severe arrhythmias, cardiorespiratory collapse, or coma did not occur. In the first infant, seizures were not present, and in the second infant, they were readily controlled with anticonvulsants.

Dose-dependent theophylline pharmacokinetics have been observed in children with asthma who were given sequential aminophylline infusions and in one patient who received a 50% overdose and had initial theophylline concentrations of about 80 μg/mL.[13] In our patient 1, who had an initial serum theophylline concentration of 76.5 μg/mL, the plot of log serum concentrations vs time was linear, so dose-dependent kinetics were not observed (Fig 1).

The half-life values in these 1-month-old infants were long compared with those of infants aged 3 to 23 months in whom the mean half-life was 4.4 hours, which is similar to the half-life in young children.[14] However, the half-life values were shorter than in premature infants who were treated with theophylline for apnea.[15-17]

In patient 2, over a range of serum theophylline concentrations of 180 to 60 μg/mL, the plots of log concentrations vs time were also linear (Fig 2), indicating the absence of dose-dependent kinetics. The scatter in the data between serum concentrations of 60 and 18 μg/mL may be due to the administration of IV fluids and changes in the volume of distribution, to spontaneous enzyme induction, or to the enzyme-inducing effect of the phenobarbital that was administered from 22 hours after the overdose. After 40 hours of treatment with phenobarbital, the plot of log theophylline concentrations vs time again became linear, with a half-life of 8.5 hours, which was 50% of the initial value. Pretreatment with phenobarbital may[18] or may not[19] enhance theophylline elimination in adult humans.

In adults, theophylline is demethylated and oxidated in vivo to 3-methylxanthine, 1,3-dimethyluric acid, and 1-methyluric acid (20), and methylation to caffeine (1,3,7-trimethylxanthine) does not occur. However, in premature neonates, methylation of theophylline at the N-7 position has been demonstrated.[21] This study confirms the fact that large doses of theophylline are also metabolized to caffeine in 1-month-old term infants as shown by increased serum caffeine concentrations that were measured by high-performance liquid chromatography and mass spectrometry. In addition, methylation may be a slower first-order metabolic pathway that masks any dose-dependent kinetics in these infants who received overdoses.

Theophylline has not been objectively evaluated in the treatment of wheezing in young infants. In our patients, wheezing disappeared at very high serum theophylline concentrations, but it recurred despite serum concentrations of 10 to 20 μg/mL, the range considered to be effective and safe for the treatment of asthma. Theophylline should be used with caution for wheezing in infants under age 3 months until its efficacy is proved or disproved and the range of effective serum concentrations and the pharmacokinetics are defined in nontoxic infants delivered at term.

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References

1. Evenson MA, Warren BL: Serum theophylline analysis by high-pressure liquid chromatography. *Clin Chem* 22:851-855, 1976.
2. Simons KJ, Simons FER, Briggs CJ, et al: Theophylline protein binding in humans. *J Pharm Sci* 68:252-253, 1979.
3. Gibaldi M, Perrier D: *Pharmacokinetics*. New York, Marcel Dekker Inc, 1975, pp 1-6.
4. White BH, Daeschner CW: Aminophylline (theophylline ethylenediamine) poisoning in children. *J Pediatr* 49:262-271, 1956.
5. Vaucher Y, Lightner ES, Walson PD: Theophylline poisoning. *J Pediatr* 90:827-830, 1977.
6. Nobel PA, Light GS: Theophylline-induced diuresis in the neonate. *J Pediatr* 90:825-826, 1977.
7. Loughnan PM, McNamara JM: Paroxysmal supraventricular tachycardia during theophylline therapy in a premature infant. *J Pediatr* 92:1016-1018, 1978.
8. Aranda JV, Dupont C: Metabolic effect of theophylline in the premature neonate. *J Pediatr* 89:833-834, 1976.
9. Zwillich CW, Sutton FD, Neff TA, et al: Theophylline-induced seizures in adults: Correlation with serum concentrations. *Ann Intern Med* 82:784-787, 1975.
10. Lawyer C, Aitchison J, Sutton J, et al: Treatment of theophylline neurotoxicity with resin hemoperfusion. *Ann Intern Med* 88:516-517, 1978.
11. Piafsky KM, Sitar DS, Rangno RE, et al: Theophylline disposition in patients with hepatic cirrhosis. *N Engl J Med* 296:1495-1497, 1977.
12. Russo ME: Management of theophylline intoxication with charcoal-column hemoperfusion. *N Engl J Med* 300:24-26, 1979.
13. Weinberger M, Ginchansky E: Dose-dependent kinetics of theophylline disposition in asthmatic children. *J Pediatr* 91:820-824, 1977.
14. Simons FER, Simons KJ: Pharmacokinetics of theophylline in infancy. *J Clin Pharmacol* 18:472-476, 1978.
15. Aranda JV, Sitar DS, Parsons WD, et al: Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 295:413-416, 1976.
16. Neese AL, Soyka LF: Development of a radioimmunoassay for theophylline: Application to studies in premature infants. *Clin Pharmacol Ther* 21:633-641, 1977.
17. Giacoia G, Jusko WJ, Menke J, et al: Theophylline pharmacokinetics in premature infants with apnea. *J Pediatr* 89:829-832, 1976.
18. Landay RA, Gonzalez MA, Taylor JC: Effect of phenobarbital on theophylline disposition. *J Allergy Clin Immunol* 62:27-29, 1978.
19. Piafsky KM, Sitar DS, Ogilvie RI: Effect of phenobarbital on the disposition of intravenous theophylline. *Clin Pharmacol Ther* 22:336-339, 1977.
20. Thompson RD, Nagasawa HT, Jenne JW: Determination of theophylline and its metabolites in human urine and serum by high-pressure liquid chromatography. *J Clin Lab Med* 84:584-593, 1974.
21. Bory C, Baltassat P, Porthault M, et al: Metabolism of theophylline to caffeine in premature newborn infants. *J Pediatr* 94:988-993, 1979.

Malformation Complex

Spondylohypoplasia, Arthrogryposis, and Popliteal Pterygium

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• Two unrelated children were born with severe congenital malformations: a girl now seven years old and a boy who died in the newborn period. Both had severe cervical hyperextension, severe flexion deformities of the limbs, and bilateral popliteal pterygia. Postmortem examination of the second case showed small, well-formed thoracic vertebrae with mild epidural fibrosis and hemorrhage. These birth defects are rare and usually occur separately. We postulate that they are related in these two cases; that the arthrogryposis and popliteal pterygia were probably the result of the spondylohypoplasia and associated changes; and that together, these related defects may constitute a new malformation complex.

(*Am J Dis Child* 134:42-45, 1980)

Spondylohypoplasia, arthrogryposis, and popliteal pterygium are rare entities that usually occur as isolated events. In 1973, Fujimoto et al[1] briefly reported an unusual case of multiple skeletal anomalies including severe cervical and thoracic spondylohypoplasia, arthrogryposis, and popliteal pterygium. A second infant, virtually identical to the first, was born at Los Angeles County-University of Southern California (LAC-USC) Medical Center. Although the first child has survived to 7 years of age, the second child died in the newborn period. The recurrence of this same constellation of birth defects suggests a common pathogenesis. These associated defects may constitute a new malformation complex.

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REPORT OF CASES

CASE 1.–A female infant was born at term to a 21-year-old healthy gravida 2, para 2 mother of Mexican-American descent. After a breech extraction delivery, the infant was transferred to LAC-USC Medical Center because of multiple congenital anomalies. At birth, the patient weighed 2,381 g. She had notable shortening of the trunk and neck and a protuberant abdomen (Fig 1). The head was hyperextended and seemed to sit directly on the shoulders. The head circumference was 33.5 cm, and the chest circumference was 32 cm. She had severe lordosis and mild scoliosis. The lower limbs had 90° flexion contractures at the knees with bilateral popliteal pterygia extending from the midthigh to calf. Both feet showed mild varus deformities. The upper limbs had flexion contractures of 30° at the elbows, flexion of the wrists, and minimal movement at the metacarpophalangeal and proximal interphalangeal joints. There were hemangiomata on the forehead, upper eyelids, nose tip, and upper lip. The right ear was posteriorly rotated and low set, and there was a cleft of the soft palate and bifid uvula.

Roentgenograms of the cervical, thoracic, and lumbosacral spine indicated posterior fusion of C2-T1, T5-T12, and L3-S2 vertebral bodies (Fig 2). The lower ribs were posteriorly crowded. There seemed to be excess thick bone along the spinous processes of the lumbar vertebral bodies and widening of the vertebral canal in this region. Except for long fingers, the bones of the limbs, skull, and hips appeared normal. Chromosomal analysis of peripheral blood showed a normal 46,XX karyotype by trypsin-Giemsa banding.

The mother used a foam contraceptive during the first trimester. She took a mixture of aspirin, phenacetin, caffeine, and pseudoephedrine hydrochloride (Emprazil) during the first month; a mixture of dicyclomine hydrochloride, doxylamine succinate, and pyridoxine hydrochloride (Bendectin) for nausea during the second month; and subcutaneous injections of epinephrine and parenteral and oral diphenhydramine hydrochloride during the third month for minor allergic reactions. She was exposed to rubella during the fifth month; however, the rubella hemagglutination inhibition titer was 1:160 at the time of exposure and three weeks later. She denied fever but reported chills on several

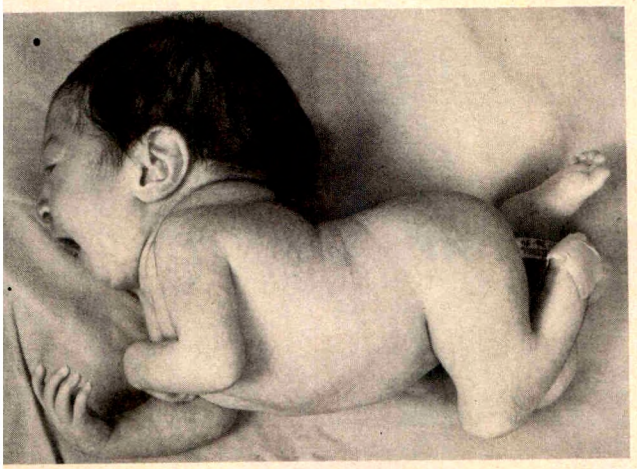

Fig 1.—Lateral view of newborn (case 1). Cervical hyperextension, severe lordosis, and flexion contractures of extremities are illustrated.

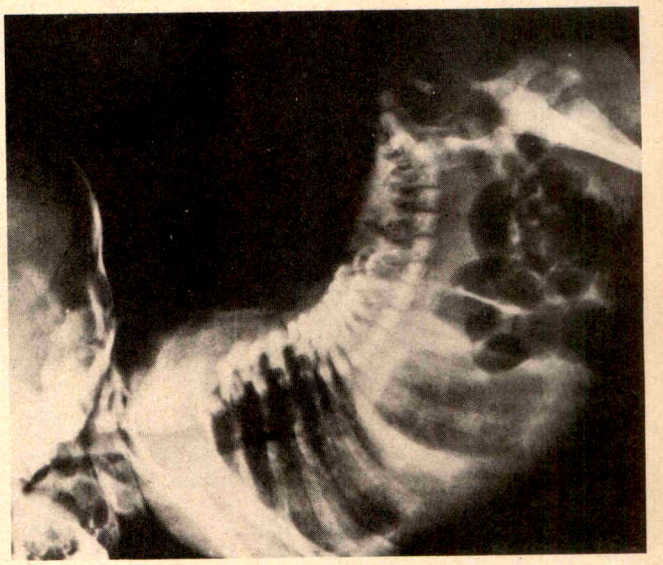

Fig 2.—Case 1. Vertebral and rib abnormalities.

occasions during the first half of pregnancy.

The father was a healthy 37-year-old Mexican-American. The union was nonconsanguineous, with one previous, healthy daughter. A maternal aunt married a paternal uncle and had five normal children. A paternal cousin had a foot abnormality of unknown type that required a brace, the only known malformation in this large kindred.

At 1 month of age, the patient was transferred to a rehabilitation hospital. At age 6 months, bilateral femoral osteotomies were performed to decrease the flexion deformities of the knees. The patient is now 7 years old, and despite intensive attempts at physical therapy, her mobility and function are severely limited. Speech is impaired because the cleft palate has not yet been repaired. Although it is difficult to evaluate her mentation and development, she socializes well and does not seem to be retarded.

Case 2.—A 2,960-g infant was born at 41 weeks' gestation. The mother was admitted to LAC-USC Medical Center in active labor with the fetus in a double footling breech presentation, and the infant was delivered by an emergency cesarean section. The Apgar scores were 1 at one minute and 2 at five minutes. Multiple skeletal anomalies were noted at birth. The baby was severely contorted with a short neck and thorax and hyperextended head (Fig 3). Small, reddish hemangiomata were present on the nose, on the upper lids, and over the eyes. The head circumference was 37.5 cm and the chest circumference was 34.5 cm. Elbows, wrists, fingers, and knees were contracted, and bilateral popliteal pterygia extended from midthigh to calf. He had long, tapering fingers held in ulnar deviation and vertical palmar creases. There was a moderate bilateral varus deformity of the feet. The palate was high arched and intact. The infant was cyanotic, and despite oxygen therapy, he became bradycardic and died at 9 hours of age in respiratory failure.

This infant was the firstborn to 21-year-old, nonconsanguineous parents. The mother had high fevers in the third or fourth month of pregnancy for which she was treated with acetaminophen. Otherwise, the pregnancy was unremarkable. Vitamins and iron were the only other medications taken. The family history was unremarkable.

Radiologic examination showed multiple abnormalities of the ribs and vertebrae, and hemivertebrae were suggested (Fig 4). Chromosomal analysis of peripheral blood lymphocytes indicated a 46,XY normal male karyotype by trypsin-Giemsa banding.

At autopsy, the multiple skeletal malformations were confirmed, but no visceral malformations were found. The lungs were atelectatic and firm, and microscopically showed congestion. The bony abnormalities of the vertebral column were striking. The cervical spine was extremely shortened so that the head sat on the shoulders in extreme dorsiflexion.

The thoracic and lumbar vertebral column was removed intact, then fixed and decalcified before sectioning. This segment measured 10 cm in overall length, and was bent at a 45° angle 4 cm from the cervical end. The portion of spinal column cephalad to the bend consisted of small, flattened vertebrae and thin, intervertebral disks. The most proximal vertebral bodies measured 2 to 3 mm in height and those closest to the bend were 3 to 4 mm in height. In the caudal portion of the vertebral column, which measured 6 cm in length beyond the bend, the vertebral bodies were of more normal size and shape and measured 7 to 8 mm in height (Fig 5).

The spinal cord within the canal was approximately 2 cm shorter than the length of the vertebral column. In the upper segment proximal to the bend, the nerve roots were obscured by dense, honeycombed, hemorrhagic fibrous tissue that was continuous with and adherent to the dura, arachnoid, and periosteum. Below the bend, the dura and meninges were unremarkable; and the nerve roots exited at the usual angle, two vertebral levels below their origin.

Microscopic examination of transverse sections through the grossly abnormal thoracic segment of the spinal cord confirmed fibrosis and hemorrhage. Acute hemorrhage was found in the dense connective tissue between dura and bone as well as surrounding the nerve roots through the intervertebral foramina. The nerves appeared intact and the dorsal root ganglia were also unremarkable. There were scattered glioblasts in the region of the anterior horn neurons that gave this area a slightly hypercellular appearance. The vertebrae were unremarkable, with a normal pattern of endochondral ossification and normal marrow.

The brain was grossly normal. Microscopic examination of sections of cerebellum, cerebrum, thalamus, medulla, and pons showed diffuse mild gliosis of cerebral white matter and mild superimposed edema. Sections of the popliteal pterygia

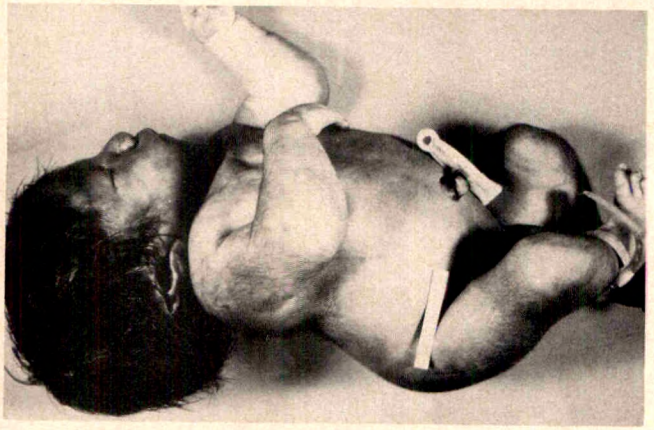

Fig 3.—Lateral view at autopsy (case 2). Hyperextended neck, lordosis, and flexion contractures of extremities are shown.

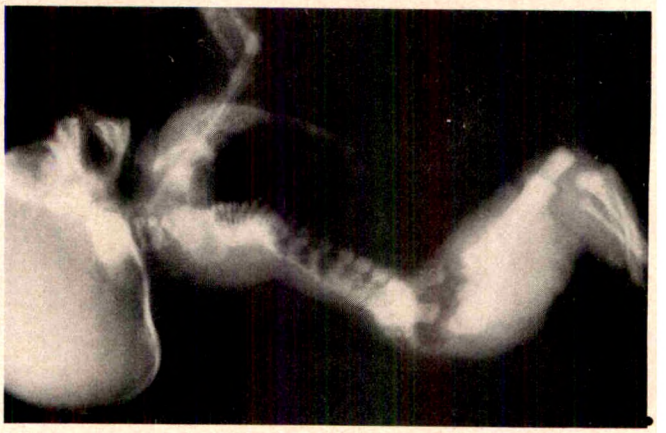

Fig 4.—Postmortem roentgenogram (case 2) of vertebral abnormalities.

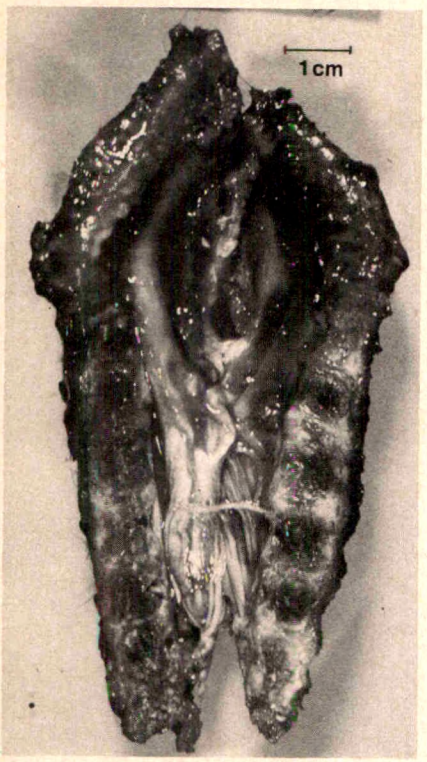

Fig 5.—Thoracic and lumbar vertebral column. Removed at autopsy and longitudinally sectioned, it illustrates hemorrhagic fibrous tissue, small thoracic vertebrae, and normal-appearing lumbar vertebrae.

consisted of nerves, vessels, and connective tissue. The remainder of the autopsy was unremarkable.

COMMENT

To explain the possible pathogenesis of the associated defects found in these two patients, the normal pattern of morphogenesis of affected parts must be understood. The early development of the human vertebral column has been extensively studied by Sensenig.[2] The definitive vertebrae of the spinal column arise from sclerotomal cells that are derived from the ventromedial and ventral aspect of the somites. A secondary sclerotome composed of the caudal half of one segment and the cranial half of the next primary sclerotome is established by the end of the fourth week of intrauterine life. The vertebrae and ribs are in turn derived from this secondary sclerotome, and the rudiments of the ribs and vertebral bodies, arches, and processes are laid down by the end of the fifth week. Chondrification begins by the sixth week, and ossification of the cartilage ensues by the end of the second month. By the end of the first trimester, the definitive shapes of both vertebrae and ribs are accomplished and ossification is well underway.

The upper limb buds begin to take shape by the end of the first month and are essentially formed by the end of the second month. The lower limbs begin about one week later and finish slightly after the arms and hands. Nonetheless, formation of the limbs is essentially complete, and their musculature and innervation well established by the end of the first trimester.[3]

By early in the second trimester when the vertebrae, ribs, and limbs are formed, an insult could impede their further growth but would not result in their malformation. In case 2, the vertebrae were found to be well formed but very small at autopsy. It is likely that the vertebral and rib abnormalities seen by roentgenographic examination of the first child represent similar anatomic alterations found at autopsy in the second case. In these two cases, the vertebral damage may be the primary event, and the rib and limb abnormalities consequent to the abnormal vertebral growth.

Although it is not possible to accurately date the time the vertebrae were damaged, their small size suggests that an injury occurred sometime early in the second trimester. Why the injury occurred only to the cervical and thoracic segments is unknown. A selective infectious or circulatory etiology is possible. It is tempting to relate the documented febrile illness of one mother early in the second trimester and the history of chills occurring sometime in the first part of pregnancy in the other mother to the pathogenesis of the malformations found in these two cases. Another remote possibility is a genetically determined mechanism, such as a new dominant mutation or an autosomal recessive disorder. How-

ever, there is no available evidence to support this hypothesis and it seems less likely.

In most cases of arthrogryposis studied, some defect of the neuromuscular system sufficient to have caused paralysis has been found.[4] In some, only microscopic evidence of decreased anterior horn cells or cerebral abnormalities could be documented. In others, grossly apparent deformities such as meningomyelocele were present. With spinal cord damage, muscle sections usually show the typical histologic pattern of denervation atrophy. But even a milder derangement of neurologic function without histologic change could account for decreased movement in utero and for arthrogryposis. This functional damage to the spinal cord's long corticospinal tracts and spinal nerves could be caused by either torsion or compromised blood supply, both of which could result from severe cervical hyperextension and thoracic deformation.

Although it is difficult to find a specific cause for the arthrogryposis in these two cases, of the various possibilities, this type of functional damage is probably the likeliest. The CNS gliosis found was mild and probably does not represent the primary insult that gave rise to the skeletal abnormalities. The acute hemorrhage found in the spinal canal was probably the result of a perinatal event, and the fibrosis in this area was most likely part of the prior injury; but, again, these changes are probably not sufficient to result in arthrogryposis. Histologic evidence of substantial cord injury was not documented and, accordingly, denervation atrophy or other skeletal muscle changes were also not found.

A popliteal pterygium represents contraction of the neurovascular bundle found at the back of the knee. It may occur as an isolated event or in association with other abnormalities. In these two cases, it probably resulted secondary to the contractures of both knees as part of the arthrogryposis multiplex congenita complex.

According to current terminology, a "malformation" is considered to be a structural abnormality of morphogenesis.[5] Sometimes, it is possible to postulate relationships between multiple malformations involving different structures, and the term "malformation complex" is used to describe such related defects. In these two cases, we postulate such a relationship between the multiple skeletal malformations. We assume the severe spondylohypoplasia probably occurred as the initial defect, and it may be the result of differentially abnormal growth of the previously well-formed cervical and thoracic vertebrae. This led in turn to the changes in the ribs and also, probably owing to functional neurologic derangement, to the arthrogryposis and popliteal pterygia.

In conclusion, we postulate that the spondylohypoplasia, arthrogryposis, and popliteal pterygia are related malformations, and together these changes constitute a new malformation complex.

References

1. Fujimoto A, Brink JD, Wilson M: Case report 10. *Syndrome Identification J* 1:14-16, 1973.
2. Sensenig EC: Early development of the human vertebral column. *Carnegie Inst Contrib Embryol* 214:21-51, 1949.
3. Moore KL: *The Developing Human*, ed 2. Philadelphia, WB Saunders Co, 1977, pp 319-326.
4. Drachman DB: The syndrome of arthrogryposis multiplex congenita. *Birth Defects* 7:90-97, 1971.
5. Smith DW: *Recognizable Patterns of Human Malformations*, ed 2. Philadelphia, WB Saunders Co, 1976, p 3.

60 Years Ago in AJDC

Dextrose Tolerance in Atrophic Infants

Clinical studies were carried out on four normal infants aged 5 to 15 months, and seven atrophic infants aged 3½ to 13 months whose weights are all well below the third percentile for their ages. Dextrose solutions of "approximately 10, 15, and 20 percent" were given by a continuous infusion pump injected intravenously over at least 30 minutes. The urine was tested for sugar with Haines' solution and was tested before the infusions and again toward or after the end of the infusion. Infused sugar was calculated as grams per kilogram per hour.

In all the normal infants glycosuria was seen at 1.0 gm/kg/hr. In none of the atrophic infants was the tolerance below 1.4 or 1.5 gm/kg/hr. In three atrophic infants glycosuria appeared first at 1.8 gm/kg/hr. Thus glucose appeared to be better tolerated in the sick than in the well infant.

The investigators suggest that "such infants might derive some benefit from intravenous glucose infusions."—P. M. Mattill; K. M. Mayer; L. W. Sauer, The Otho S. A. Sprague Memorial Institute Laboratory, Children's Memorial Hospital, Chicago (19:42, January 1920).

Changes in Zinc Metabolism During the Course of the Nephrotic Syndrome

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• **The plasma zinc concentration and quantitative urinary zinc excretion were studied in 105 pediatric patients with the nephrotic syndrome or nephritis-nephrosis. The plasma level was decreased to a mean value of 51.7 μg/dL in patients with the nephrotic syndrome (controls, 85 μg/dL). The rate of urinary zinc excretion was not different from that of the controls, with the exception of patients whose disease was in the polyuric phase of beginning remission where it was fivefold higher and those who had achieved a long-lasting remission of the disease. Since about two thirds of the plasma zinc is bound to albumin, an unchanged zinc-albumin ratio would reflect an equal zinc and albumin loss. The ratio, however, was increased twofold and thus does not adequately explain the hypozincemia. The low hair level of 86 μg/g may suggest a more profoundly disturbed zinc metabolism than originally thought.**

(*Am J Dis Child* 134:46-50, 1980)

Our interest in studying the plasma concentration and excretory rate of zinc in patients with nephrotic syndrome was stimulated by two observations. In 1942, McCance and Widdowson[1] described two patients with albuminuria that was accompanied by a substantially increased zinc excretory rate. In contrast, Fairhall and Hoyt[2] had found earlier an essentially unchanged rate of zinc excretion in nephritis or nephrosis. In 1972, when studying the aminonucleoside nephrosis of rats, Freeman et al[3] observed an increase in the rate of zinc excretion almost parallel to the increase in the rate of protein excretion. At the same time, the plasma zinc levels decreased below normal. The second observation refers to studies of Flynn et al[4] who reported a precipitous decrease in serum zinc concentration during corticosteroid treatment and who suspected a relation to the adrenocorticotropic hormone production or corticosteroid secretion.

We decided, therefore, to study changes in the metabolism of zinc in patients with the nephrotic syndrome, a disease that by definition is accompanied by substantial proteinuria. In addition, most pediatric patients with the nephrotic syndrome receive prolonged corticosteroid treatment. Our results show that the plasma zinc level is decreased in patients with the nephrotic syndrome as long as proteinuria is present. The rate of urinary zinc excretion, however, is not increased and shows little change during the course of the nephrotic syndrome.

SUBJECTS AND METHODS

A total of 105 pediatric patients who fulfilled the criteria for the nephrotic syndrome (anasarca, proteinuria, hypoalbuminuria, hypercholesterolemia), or glomerulonephritis and nephrotic syndrome (proteinuria, persistent hematuria, transient or constant mild hypertension) were included in this study. They were separated into two groups, 81 patients with idiopathic nephrotic syndrome and 24 patients with a combination of nephritis-nephrosis. Studies were also performed in seven patients with glomerulonephritis, but because of the small number, the data were not included in the statistical evaluation. Selected results are given in this report. These patients were compared with a group of 33 healthy children of corresponding age who were recruited from healthy siblings of our patients. In each instance, including the healthy controls, a 24-hour urine collection and blood and hair samples were obtained. The majority of our patients and all control subjects were not hospitalized at the time of this study. The mean age was 7 years (range, 1 to 16 years). The diagnosis of nephritis-nephrosis represents cases of early membranoproliferative glomerulonephritis, focal glomerulosclerosis, and membranous and diffuse proliferative glomerulonephritis. The renal function as measured by creatinine clearance or serum creatinine level was not substantially decreased in these cases.

The patients also were grouped according to their disease activity, as determined by presence or absence of proteinuria, and

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vere separated into different treatment groups. In the majority of cases, the disease progressed from an initial state where proteinuria was present but treatment had not been started (group 1) to the point where proteinuria was still evident but treatment with prednisone (2 to 3 mg/kg/24 hr) was also given (groups 2 and 3). In group 2, patients are listed who received daily prednisone administration, whereas patients who were changed to a Monday-Wednesday-Friday treatment schedule were entered into group 3.

Remission of the disease was characterized by a return of the urinary protein excretory rate to less than 150 mg/24 hr (groups 4 to 6). Again, the results were categorized into three groups, patients who received daily prednisone therapy (group 4), who received intermittent prednisone administration (group 5), or who did not require any treatment (group 6). Patients with the additional diagnosis of glomerulonephritis were assigned to the same groups although corticosteroid treatment was used much less frequently. A dietary history was not obtained in our patients or the controls.

The quantitative excretion or the concentration of zinc in urine, plasma, and hair was studied in our patients. At the same time, the rate of excretion of creatinine and protein and the serum concentration of total protein, albumin, α_2-globulin, and creatinine were measured. Hair samples were obtained from the occipital area, with the hair cut close to the scalp and the proximal 2 cm used for analysis (20 to 60 mg of hair). Hair samples were washed with nonionic detergent and deionized water and, prior to chemical determination, were ashed in concentrated nitric acid. The amount of zinc was determined by atomic absorption spectrophotometry according to a modification of the method of Meret and Henkin,[5,6] total protein by the use of biuret reagent according to a modification of the method as published by Mattenheimer,[7] and serum protein fractions by protein electrophoresis using cellulose acetate electrophoresis. The mean and SD were calculated for the data of each group, and the level of significance was calculated for each set of data.

RESULTS

Zinc and Protein Levels in Plasma

All patients with the nephrotic syndrome or a combination of nephritis and nephrosis had decreased serum total protein and albumin levels but increased α_2-globulin concentrations (Table 1). They maintained low serum protein and albumin levels as long as proteinuria was present, even during corticosteroid therapy. During active disease, the mean serum albumin level in patients with nephrotic syndrome was 1.7 g/dL (control, 4.0 g/dL). At the same time, the α_2-globulin concentration was increased to 1.42 g/dL (control, 0.6 g/dL).

The plasma zinc concentration was also low in all children with active nephrotic syndrome or nephritis-nephrosis (mean, 50 and 52 μg/dL, respectively) (Fig 1), whereas all patients with glomerulonephritis maintained a normal level (79 ± 14.5 μg/dL). With improvement in the disease condition, an increase in plasma zinc concentration was observed, particularly in children in disease remission, although the level remained slightly low (mean, 69 μg/dL) in most cases.

To test the relationship between plasma zinc and serum protein or

Table 1.—Serum Values of Children With the Nephrotic Syndrome and Nephritis-Nephrosis*

Group	Mean Values, g/dL (SD)		
	Total Protein	Albumin	α_2-Globulin
Control			
(n = 33)	6.8 (1.0)	4.0 (1.0)	0.6 (0.3)
Nephrotic Syndrome			
1 (n = 48)	4.9† (1.2)	1.7‡ (1.0)	1.38 (0.6)
2 (n = 62)	4.7 (1.7)	1.35‡ (1.0)	1.48† (0.7)
3 (n = 36)	5.0 (1.9)	2.1‡ (1.0)	1.02 (0.6)
4 (n = 72)	6.3 (1.0)	3.3 (1.1)	1.15 (0.5)
5 (n = 49)	6.8 (0.9)	4.1 (0.6)	0.80 (0.4)
6 (n = 26)	6.3 (0.9)	3.3† (0.7)	0.62 (0.2)
Nephritis-Nephrosis			
1 (n = 18)	5.1 (1.6)	1.85‡ (1.2)	1.37† (0.5)
2 (n = 10)	4.5 (1.4)	1.7‡ (1.25)	1.58‡ (0.7)
3 (n = 11)	4.6 (2.1)	2.15† (1.1)	0.85 (0.45)

*Patients are grouped according to level of treatment.
†$P < .05$, as compared with controls.
‡$P < .01$, as compared with controls.

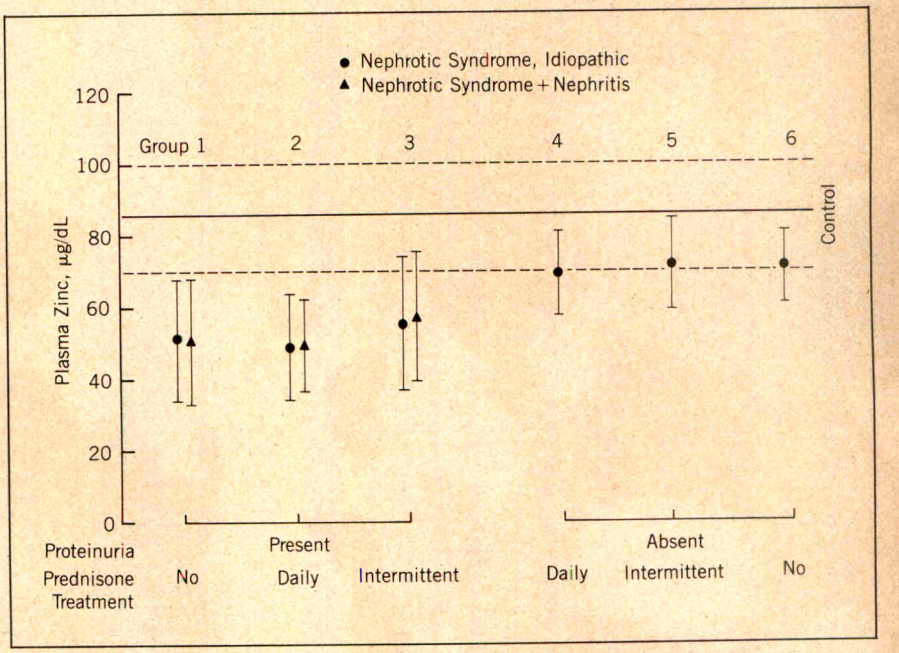

Fig 1.—Concentration of zinc in plasma is decreased in children with active nephrotic syndrome and those with combined nephritis-nephrosis. In cases of normal protein excretion, plasma level is slightly low although not significantly different from controls, shown as mean and SD (dotted lines).

Table 2.—Plasma Zinc-Protein Ratios of Children With the Nephrotic Syndrome and Nephritis-Nephrosis

Group	Mean Values, μg/g (SD)		
	Zn-Protein	Zn-Albumin	Zn-α_2-Globulin
Control			
(n = 33)	12.5 (2.0)	21.2 (7.0)	141.7 (30.0)
Nephrotic Syndrome			
1 (n = 42)	10.6 (3.1)	37.6* (19.8)	49.0† (34.2)
2 (n = 59)	10.5 (3.6)	46.7* (20.4)	38.8† (24.7)
3 (n = 68)	10.7 (2.0)	36.8* (18.4)	61.0† (29.6)
4 (n = 45)	10.8 (2.0)	21.9 (8.2)	65.4† (23.2)
5 (n = 34)	11.0 (1.8)	19.0 (5.5)	103.5 (26.2)
6 (n = 20)	11.3 (2.1)	20.3 (6.4)	113.2 (28.0)
Nephritis-Nephrosis			
1 (n = 16)	9.9 (3.1)	38.4 (22.2)	51.8† (24.3)
2 (n = 10)	10.7 (2.5)	43.1* (18.9)	35.4† (20.5)
3 (n = 10)	10.8 (2.5)	33.7 (15.0)	76.0† (29.4)

*$P < .05$, as compared with controls.
†$P < .01$, as compared with controls.

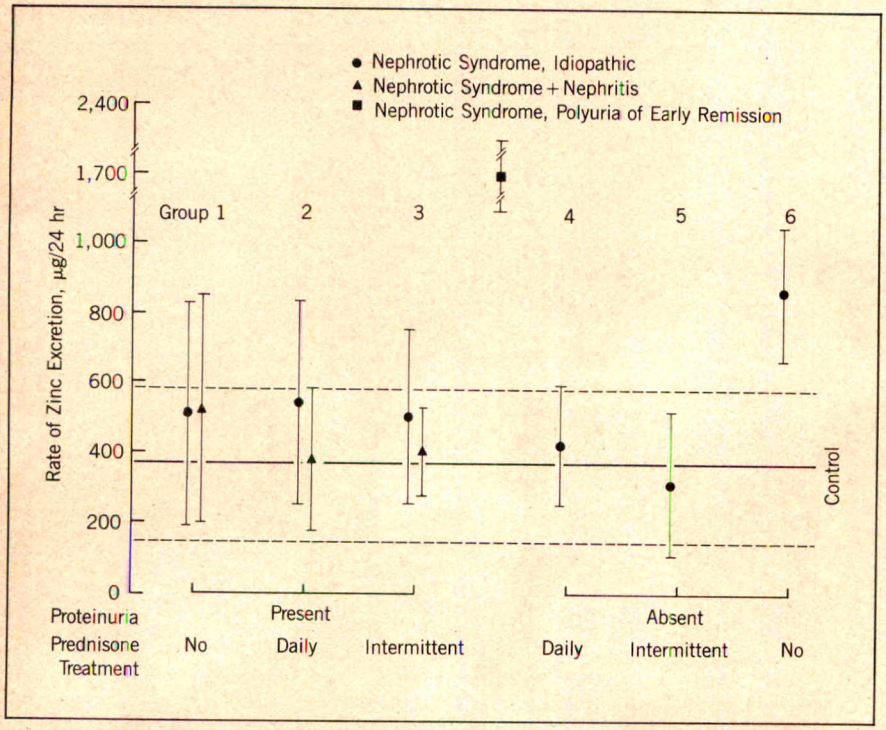

Fig 2.—Quantitative excretion of zinc is not different in children with nephrotic syndrome from that of controls with two exceptions: in patients during polyuric phase of beginning disease remission and in patients no longer receiving treatment and free of disease, rate of zinc excretion is significantly elevated.

protein fractions, the ratio between zinc and total protein, albumin, or α_2-globulin was calculated (Table 2). The latter two are the two major plasma protein fractions that bind and transport zinc. Table 2 gives the ratio of zinc to total protein as slightly but not significantly lower in patients with proteinuria than in controls. On the other hand, the zinc-albumin ratio increased during proteinuria more than twofold compared with the controls and decreased only after excessive proteinuria had ceased. We also observed a threefold decrease in the zinc-α_2-globulin ratio in almost all groups. In children in remission and no longer receiving therapy, however, the value was not significantly different from that of controls (Table 2).

Table 3.—Rate of Protein Excretion and Urinary Zinc-Creatinine Ratio in Children With the Nephrotic Syndrome and Nephritis-Nephrosis

Group	Mean Values (SD)	
	Quantitative Urinary Protein Excretory Rate, g/24 hr	Urinary Zn-Creatinine Ratio, μg/g
Control		
(n = 33)	0.08 (0.05)	0.6 (0.3)
Nephrotic Syndrome		
1 (n = 50)	2.34* (0.78)	3.3† (2.6)
2 (n = 64)	1.86* (1.1)	2.9† (2.1)
3 (n = 40)	1.20* (0.6)	5.9* (3.0)
4 (n = 78)	0.07 (0.04)	1.1 (0.6)
5 (n = 53)	0.09 (0.03)	0.7 (0.2)
6 (n = 29)	0.1 (0.02)	0.9 (0.3)
Nephritis-Nephrosis		
1 (n = 20)	2.04* (1.0)	1.4 (0.9)
2 (n = 15)	1.22* (0.66)	0.9 (0.3)
3 (n = 14)	1.81* (0.95)	1.0 (0.2)

*$P < .01$, as compared with controls.
†$P < .05$, as compared with controls.

Urinary Excretion of Zinc and Protein

The mean rate of protein excretion in patients with the nephrotic syndrome was 2.3 g/24 hr (range, 0.6 to 5.7 g/24 hr) during active disease. Overall, there was no significant difference between children with "minimal change" nephrotic syndrome and those who had an underlying glomerulonephritis although there was considerable individual variability. In patients with nephrotic syndrome, the proteinuria remained essentially unchanged as long as the disease was active and was independent of prednisone treatment (Table 3). Patients whose disease was in remission had, by definition, a normal protein excretion.

The quantitative zinc excretion in children with nephrotic syndrome or nephritis-nephrosis was significantly ($P < .01$) elevated in only two groups (Fig 2). Children who underwent massive diuresis during early remission excreted zinc in quantities up to 2,500 μg/24 hr (mean, 1,895 μg/24 hr), an amount that is several times that of the corresponding controls. Also, patients whose disease was in complete remission and who were no longer receiving steroid therapy excreted about twice as much zinc as the controls.

Important information may be obained from the ratio of zinc to protein n the urine (Fig 3). This ratio was low n all children with proteinuria).9 ± 0.8 μg/mg) and increased bout eightfold to tenfold to 8.3 ± 5.8 g/mg in patients with normal proein excretion.

Hair Zinc Content

The mean hair zinc level was 86 g/g, with values ranging as low as 49 g/g for our patients with nephrotic yndrome or nephritis-nephrosis as ompared with a level of 125 to 150 g/g for control children of the same ge (Fig 4). Similarly, low levels were ound for children who had stopped eceiving prednisone treatment after hey had achieved remission of the lisease for nine to 12 months. Patients with glomerulonephritis, owever, had normal hair zinc concenrations.

COMMENT

The plasma zinc level was decreased n our patients with the nephrotic yndrome as long as proteinuria was present. The same observation was eported during the course of the minonucleoside nephrosis of rats.[3] An increase occurred in remission, but he level remained low even in patients who were free of disease for an extended time period. To find an explanation for the low plasma zinc concentration, we have studied the relation between zinc and important plasma protein fractions. Essentially all plasma zinc is protein-bound, about 30% firmly to an α_2-macroglobulin,[8-10] the remainder loosely to either albumin (about 60%) or other low molecular weight complexes (about 10%). The exact ratio of these plasma zinc fractions is still in dispute.[11-13] We found an increase in the serum zinc-albumin ratio in the presence of proteinuria that indicates a proportionately larger albumin loss. The concentration of the second important transport protein, serum α_2-globulin, was increased compared with that of zinc. The zinc-globulin ratio was threefold lower in the nephrotic patients than in the controls, and it was slightly decreased even in children whose disease was in complete

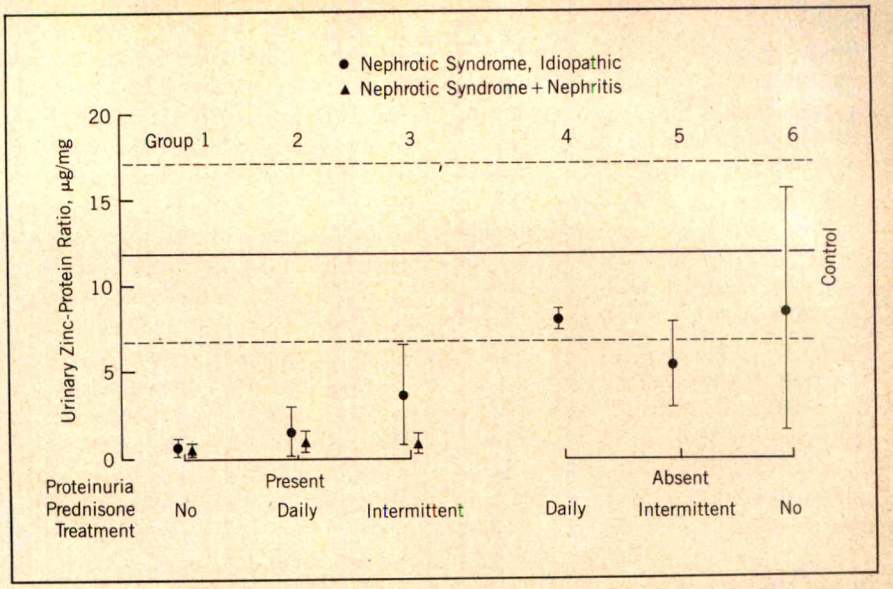

Fig 3.—Zinc-protein ratio in urine is significantly lower for patients with nephrotic syndrome than for control patients as long as proteinuria is present. As soon as proteinuria has ceased, value is not significantly different from that of controls.

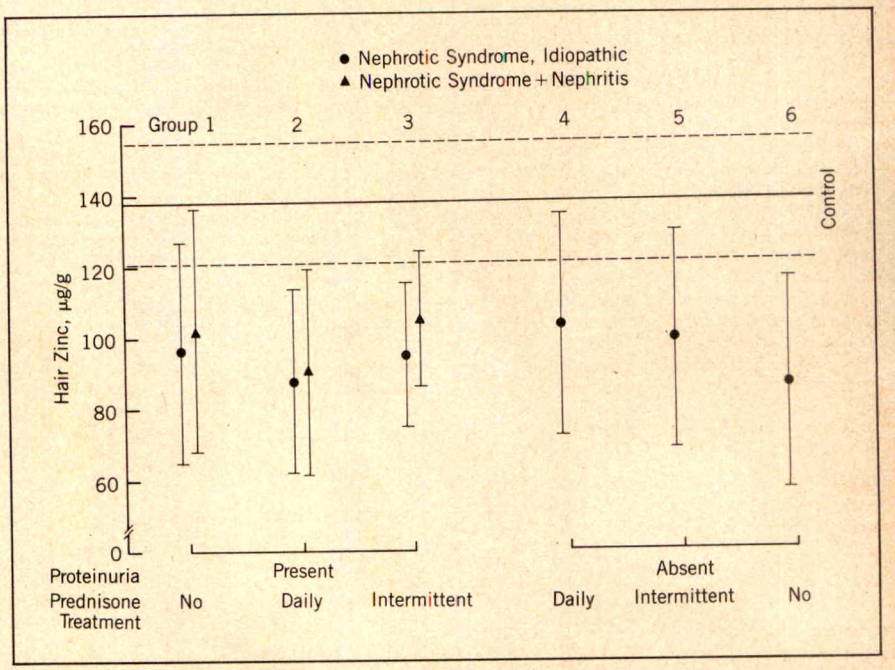

Fig 4.—Concentration of zinc in hair of patients with nephrotic syndrome or nephritis-nephrosis is decreased throughout entire observation period as compared with control patients. Difference is statistically significant ($P < .05$).

remission. These two findings speak against the assumption that the hypozincemia is correlated to changes in these important zinc transport proteins despite the fact the zinc-total protein ratio remained unchanged.

Also, we found that prednisone treatment did not lower the plasma zinc concentration. We could not document a difference between children treated with prednisone and those who did not receive prednisone treatment as long as their disease was in a comparable stage. The observation of Flynn et al[4] to the contrary may be explained by the fact that our patients received this hormone for a long period of time, allowing for a gradual correction of acute changes.

In our study, the low plasma zinc

level could not be explained by an increased rate of urinary zinc excretion. In fact, the urinary zinc excretory rate showed little change during the course of the nephrotic syndrome. This is in contrast to the brief report of McCance and Widdowson[1] and to the results of the aminonucleoside nephrosis study in rats.[3] Only Fairhall and Hoyt[2] reported an unchanged rate of zinc excretion in patients with nephritis or nephrosis. Two points, however, require mentioning: (1) In seven patients whose disease was in the polyuric phase of beginning disease remission, a threefold to fourfold increase in the zinc excretory rate was observed, which probably lasted only for a short period because the rate of zinc excretion was found to be low in all children whose disease was in complete remission. (2) The urinary zinc excretory rate was higher in children who had achieved a full, long-lasting remission and who were not receiving steroid treatment than in control patients. Dietary factors are an unlikely explanation for the increased rate of zinc excretion. Although some pathologic conditions like starvation or excessive zinc administration are known to increase the rate of urinary zinc excretion in a healthy subject,[14] the renal zinc excretion plays only an insubstantial role in maintaining the zinc balance. At least 80% of the ingested zinc is eliminated through the gastrointestinal tract, and less than 10% is excreted in the urine.[15] Moderate dietary changes of zinc intake are not reflected in an increased rate of urinary zinc excretion. All these factors suggest that additional, presently unknown factors exert an influence on the zinc balance in patients with the nephrotic syndrome.

Finally, the low zinc concentration in hair of most patients with the nephrotic syndrome or nephritis-nephrosis may suggest a more profoundly disturbed zinc balance than was thought. This question could not be answered with the information available from this study and is presently under investigation.

Deborah J. Besch and Paula Thompson provided secretarial aid, and they have carried out and completed this research.

References

1. McCance RA, Widdowson EM: The absorption and excretion of zinc. *Biochem J* 36:692-696, 1942.

2. Fairhall LT, Hoyt LH: The excretion of zinc in health and disease. *J Clin Invest* 7:537-541, 1929.

3. Freeman RM, Richards CJ, Rames LK: Zinc metabolism in nephrotic rats. *Circulation* 46 (suppl 2):72, 1972.

4. Flynn A, Pories WJ, Strain WH, et al: Rapid serum-zinc depletion associated with corticosteroid therapy. *Lancet* 1169-1172, 1971.

5. Reimold EW, Besch DJ: Detection and elimination of contaminations interfering with the determination of zinc in plasma. *Clin Chem* 24:657-680, 1978.

6. Meret S, Henkin RI: Simultaneous direct estimation by atomic absorption spectrophotometry of copper and zinc in serum, urine, and cerebrospinal fluid. *Clin Chem* 17:369-373, 1971.

7. Mattenheimer H: *Micromethods for the Clinical and Biochemical Laboratory.* Ann Arbor, Ann Arbor Science Publishers Inc, 1970, pp 74-77.

8. Parisi AF, Vallee BL: Isolation of a zinc α_2-macroglobulin from human serum. *Biochemistry* 9:2421-2426, 1970.

9. Giroux EL: Determination of zinc distribution between albumin and α_2-macroglobulin in human serum. *Biochem Med* 12:258-266, 1975.

10. Burns RR, Fell GS: Estimation and interpretation on plasma zinc fractions. *Scot Med J* 21:153-154, 1976.

11. Prasad AS, Oberleas D: Binding of zinc to amino acids and serum proteins in vitro. *J Lab Clin Med* 76:416-425, 1970.

12. Henkin RI: Metal-albumin-amino acid interactions: Chemical and physiological interrelationships. *Adv Exp Med Biol* 48:299-328, 1973.

13. Burch RE, Hahn KJ, Sullivan JF: Newer aspects of the roles of zinc, manganese, and copper in human nutrition. *Clin Chem* 21:501-520, 1975.

14. Spencer H, Osis D, Kramer L, et al: Intake, excretion, and retention of zinc in man, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease.* New York, Academic Press Inc, 1976, pp 345-361.

15. Zinc in humans, in *Zinc: Subcommittee on Zinc Division of Medical Sciences Assembly of Life Sciences National Research Council.* Baltimore, University Park Press, 1979, pp 123-172.

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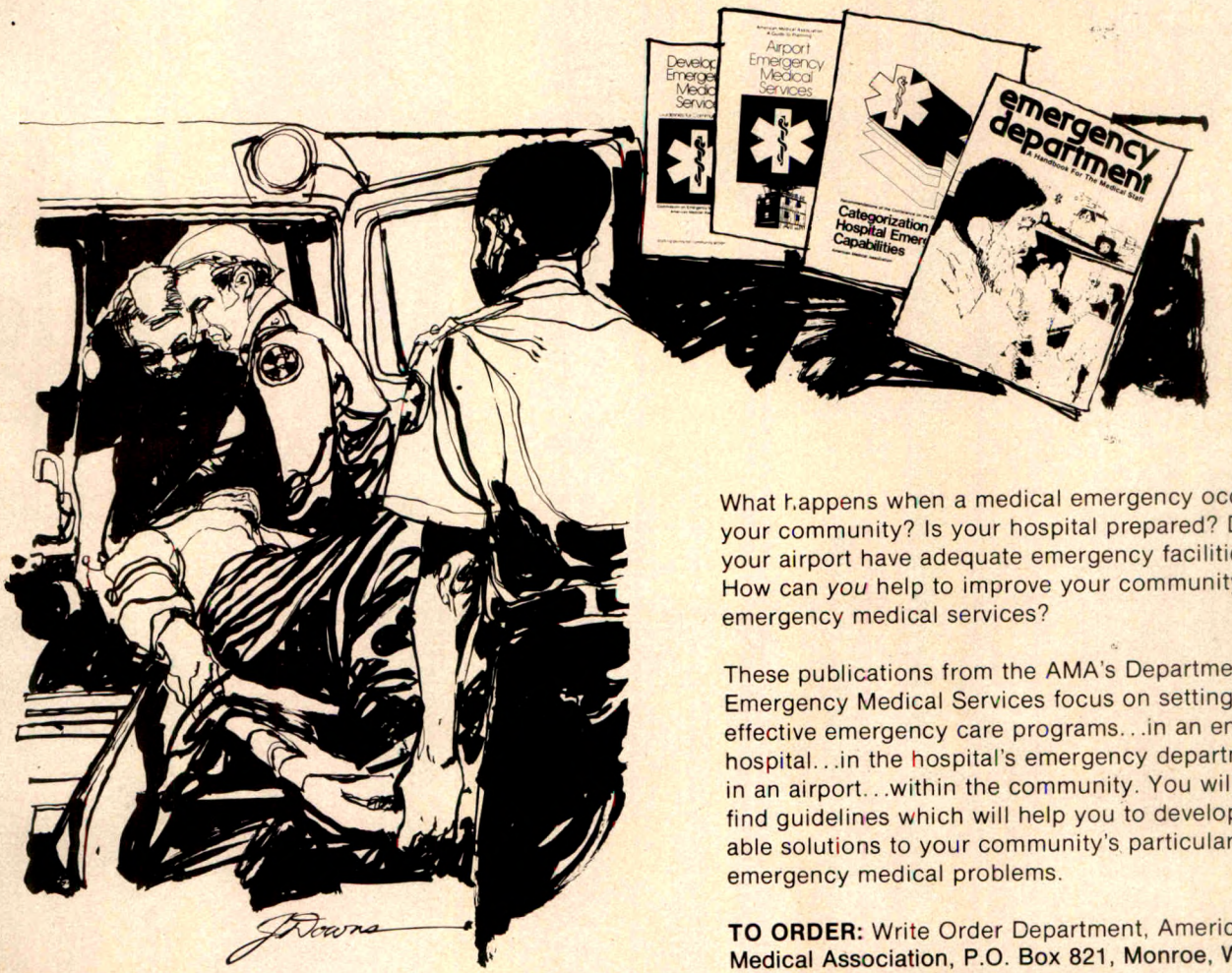

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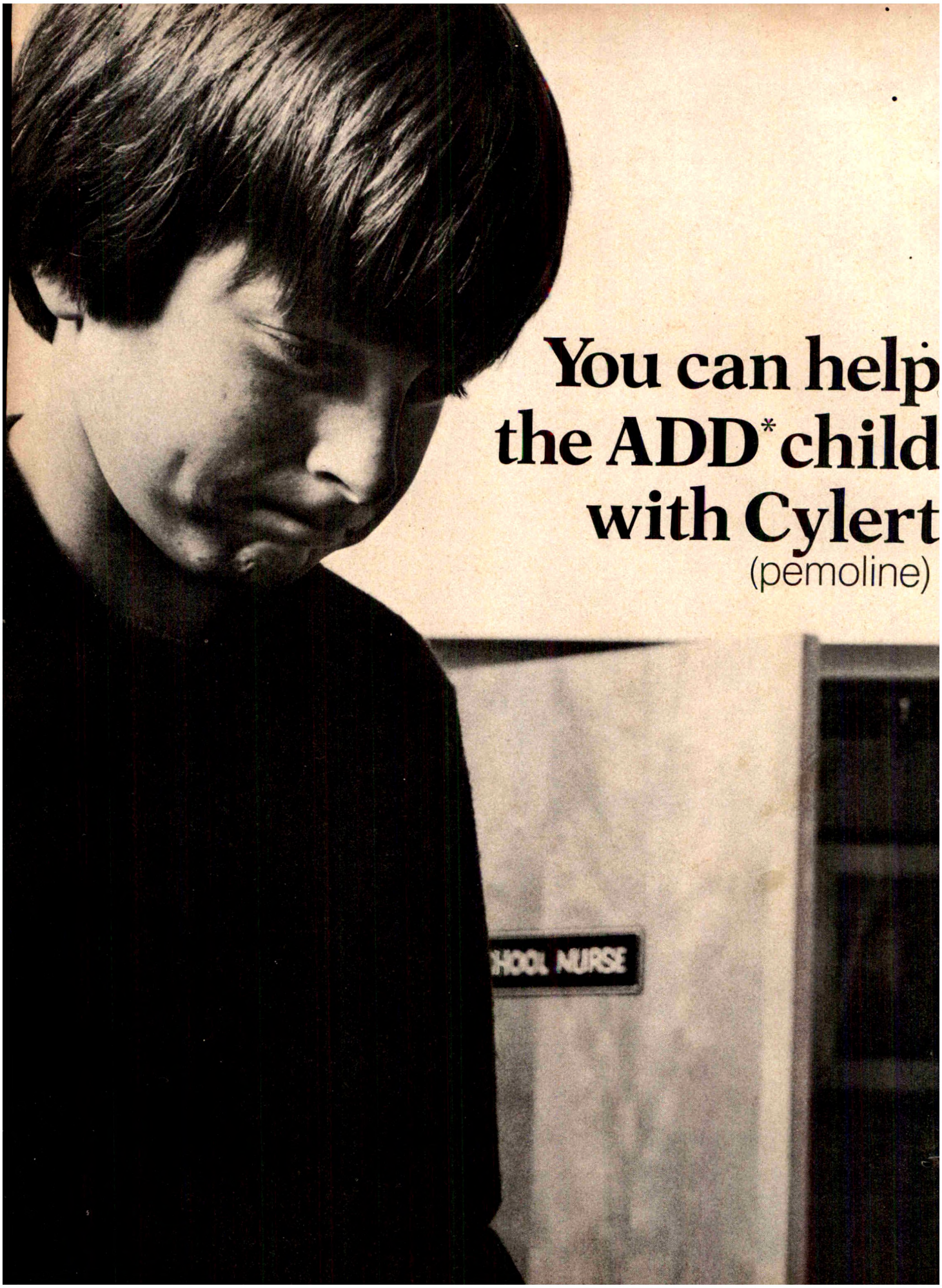

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Cylert avoids problems of taking a drug at school. No involvement of school personnel. No peer teasing about noon-time dosing. The parents manage all medication, and the child carries no drugs. (And note that Cylert is Schedule IV, not II.)

Cylert® (pemoline) **C IV**

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Just once a day. At home.

*ADD: Attention Deficit Disorder (formerly called MBD, Minimal Brain Dysfunction), or the Hyperkinetic Syndrome. Please see next page for Brief Summary.

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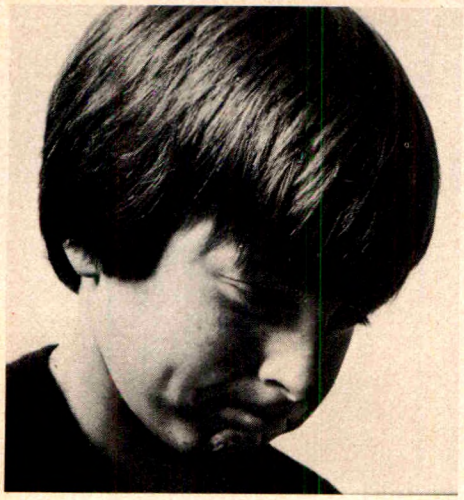

Day-long behavior therapy without dosing problems at school

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Brief Summary of Prescribing Information

INDICATIONS—CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS—CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS—CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS—Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS—Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE—Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION—CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

HOW SUPPLIED—CYLERT (pemoline) is supplied as monogrammed, grooved tablets in three dosage strengths:

18.75 mg. tablets (white) in bottles of 100 (**NDC** 0074-6025-13)
37.5 mg. tablets (orange-colored) in bottles of 100 (**NDC** 0074-6057-13)
75 mg. tablets (tan-colored) in bottles of 100 (**NDC** 0074-6073-13)

CYLERT Chewable is supplied as monogrammed, grooved tablets in one dosage strength:

37.5 mg. tablets (orange-colored) in bottles of 100 (**NDC** 0074-6088-13)

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1. Lewis Webster, Ph.D. (Cantab.), B.Sc., M.A.A.C.B., "Cystic Fibrosis Screening By Sweat Analysis," *Medical Journal of Australia*, 1977, 1:923-927.

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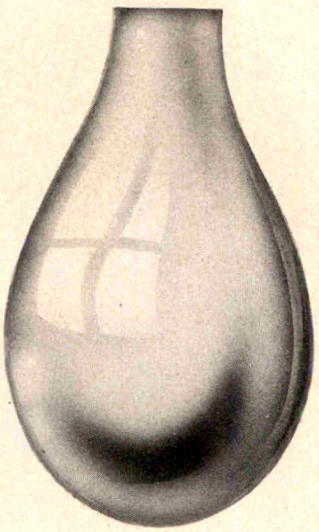

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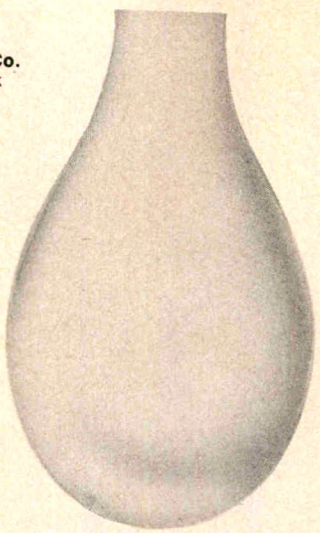

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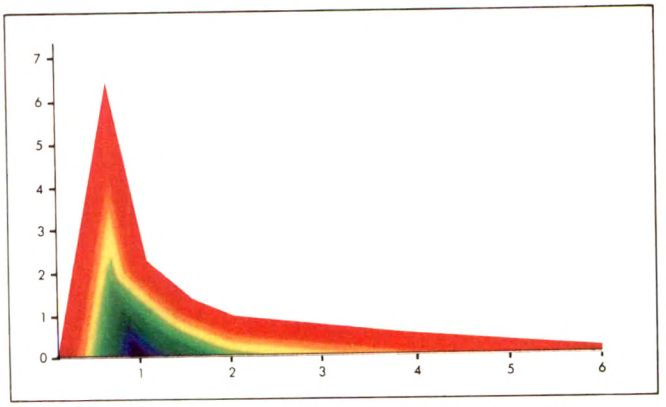

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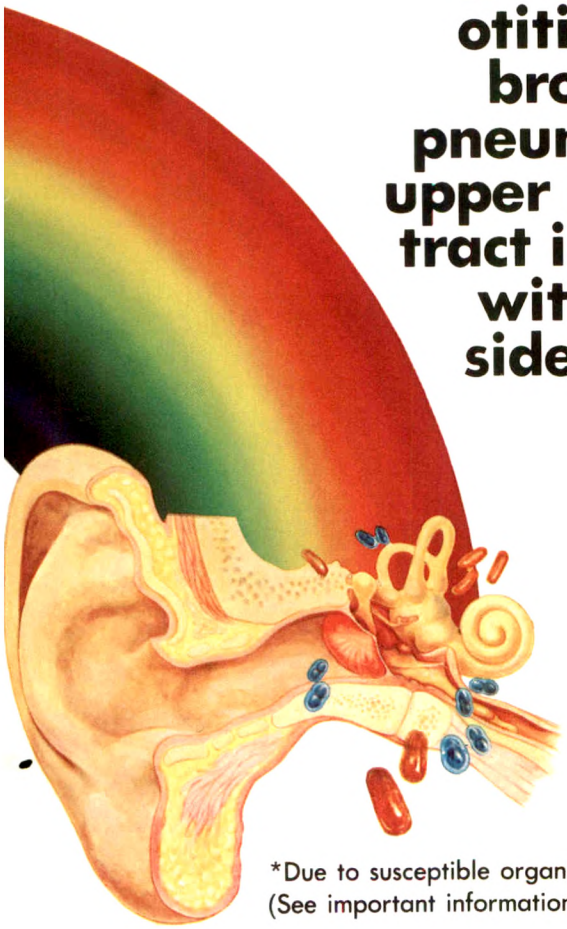

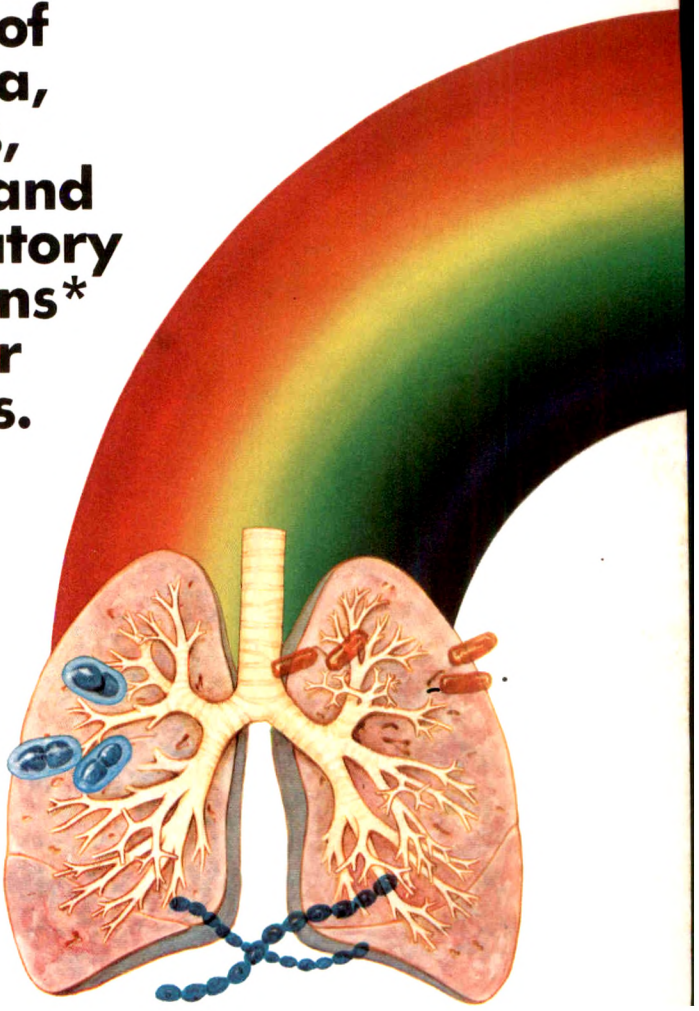

*Due to susceptible organisms
(See important information on last page.)

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efficacy with fewer side
ampicillin confirmed in
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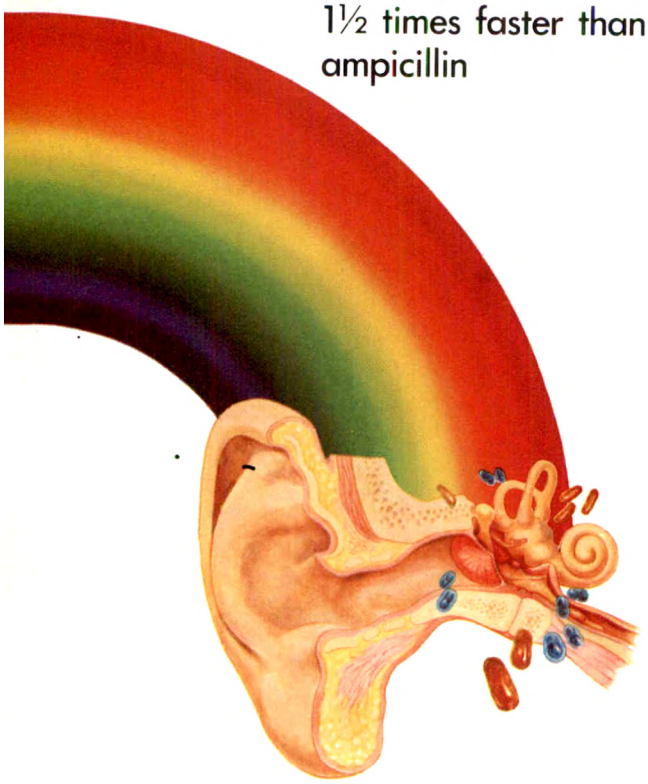
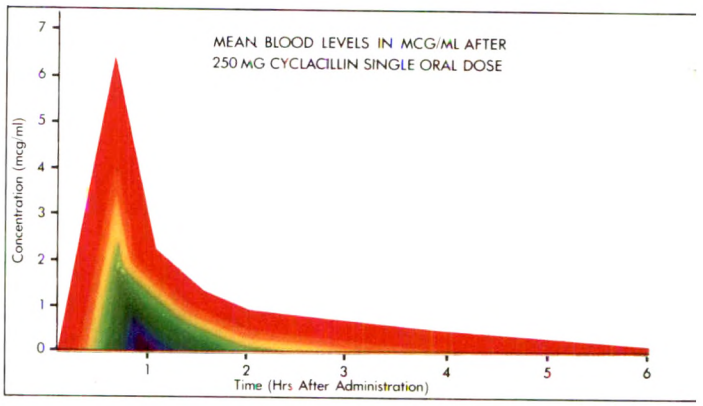
Rapid, virtually complete absorption from GI tract

Rapid onset of action—mean peak serum levels within 30 minutes

Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)

Rapidly excreted unchanged in the urine—1½ times faster than ampicillin





Clinical efficacy of CYCLAPEN® in otitis media†

Causative Organism		No. of Patients
S. pneumoniae	96 % Clinical Response 95 % Bacterial Eradication	82
H. influenzae	88 % Clinical Response 85 % Bacterial Eradication	96

more than just spectrum in otitis media

*Includes all patients treated. 2,415 evaluated for safety; 1,819 evaluated for efficacy.

†Due to susceptible organisms.

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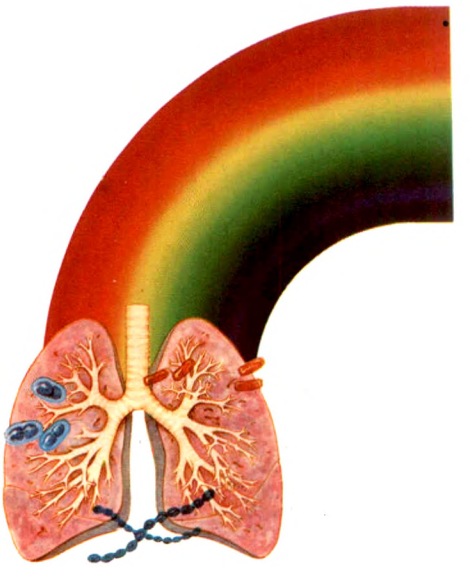
ffects than louble-blind patients*



wer side effects with CYCLAPEN® in uble-blind studies to date[1,2]

Total number of drug-related side effects in all patients	
CYCLAPEN®	128 of 1,286 (10%) of patients
ampicillin	202 of 1,129 (18%) of patients
Difference statistically significant (P <0.001)	

In bronchitis, pneumonia and upper respiratory tract infections†

High cure rate with CYCLAPEN®		
Causative Organism	Bronchitis/Pneumonia†	No. of Patients
S. pneumoniae	100 / 95	73
Chronic Bronchitis† (acute exacerbation)		
H. influenzae	92 — Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*	12
Streptococcal Sore Throat†		
Group A beta-hemolytic Streptococcus	100 / 86	44
% Clinical Response % Bacterial Eradication		

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Excellent clinical results in eliminating the two most common causative organisms in otitis media

Significantly lower incidence of diarrhea and skin rash in children treated with CYCLAPEN® Suspension

	diarrhea	rash
CYCLAPEN	9.1%	2.1%
ampicillin	19.2%	5.8%
	P < 0.001	P < 0.03

more than just spectrum CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Gold JA, Hegarty CP, Deitch MW, Walker BR: Double-blind clinical trials of oral cyclacillin and ampicillin, *Antimicrob Ag Chemother* 15:55-58, (Jan.) 1979.

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See important information on next page.)

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New from Wyeth Laboratories

CYCLAPEN®
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Usual children's dosage: 50 to 100 mg/kg/day in equally spaced doses, depending on severity.

more than just spectrum in otitis media, bronchitis, pneumonia, and upper respiratory tract infections*

- Rapid, virtually complete absorption from GI tract
- Rapid onset of action—mean peak serum levels within 30 minutes
- Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)
- Rapidly excreted unchanged in the urine—1½ times faster than ampicillin
- Significantly fewer episodes of diarrhea and skin rash than reported with ampicillin in studies to date
- Excellent clinical response and outstanding bacterial eradication documented in double-blind studies involving 2,581 patients
- New CYCLAPEN®
  - Suspension—great-tasting raspberry punch flavor

*Due to susceptible organisms.

How Supplied

CYCLAPEN® (cyclacillin) tablets:
250 mg scored tablets
500 mg scored tablets

Indications

Cyclapen® (cyclacillin) has less in vitro activity than other drugs in the ampicillin class of antibiotics and its use should be confined to the indications listed below.

Cyclapen® is indicated for the treatment of the following infections:

RESPIRATORY TRACT
Tonsillitis and pharyngitis caused by Group A beta-hemolytic streptococci
Bronchitis and pneumonia caused by *S. pneumoniae* (formerly *D. pneumoniae*)
Otitis Media caused by *S. pneumoniae* (formerly *D. pneumoniae*) and *H. influenzae*
Acute exacerbation of chronic bronchitis caused by *H. influenzae**
*Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*.

SKIN AND SKIN STRUCTURES (integumentary) infections caused by Group A beta-hemolytic streptococci and staphylococci, non-penicillinase producers.

URINARY TRACT INFECTIONS caused by *E. coli* and *P. mirabilis*. (This drug should not be used in any infections caused by *E. coli* and *P. mirabilis* other than urinary tract infections.)

NOTE: Cultures and susceptibility tests should be performed initially and during treatment to monitor the effectiveness of therapy and the susceptibility of bacteria. Therapy may be instituted prior to the results of sensitivity testing.

Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to penicillins.

Warnings

CYCLACILLIN SHOULD ONLY BE PRESCRIBED FOR THE INDICATIONS LISTED IN THIS INSERT.

CYCLACILLIN HAS LESS *IN VITRO* ACTIVITY THAN OTHER DRUGS OF THE AMPICILLIN CLASS ANTIBIOTICS. HOWEVER, CLINICAL TRIALS HAVE DEMONSTRATED THAT IT IS EFFICACIOUS FOR THE RECOMMENDED INDICATIONS.

SERIOUS AND OCCASIONAL FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING PENICILLIN.

ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL ADMINISTRATION, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE ARE REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY REACTIONS WHO EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH A CEPHALOSPORIN. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE ABOUT PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY SHOULD BE INITIATED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

PREGNANCY: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to ten times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cyclacillin is administered to a nursing woman.

Adverse Reactions

The oral administration of cyclacillin is generally well tolerated.

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated

CYCLAPEN® (cyclacillin) for oral suspension
125 mg per 5 ml:
100 ml and 200 ml bottles
250 mg per 5 ml:
100 ml and 200 ml bottles

hypersensitivity to penicillins or in those with a history of allergy, asthm fever, or urticaria.

The following adverse reactions have been reported with the use of cycl diarrhea (in approximately 1 out of 20 patients treated), nausea and vo (in approximately 1 in 50), and skin rash (in approxrmately 1 in 60). Is instances of headache, dizziness, abdominal pain, vaginitis, and urticari been reported. (See WARNINGS)

Other less frequent adverse reactions which may occur and that have reported during therapy with other penicillins are: anemia, thrombocyto thrombocytopenic purpura, leukopenia, neutropenia and eosinophilia. reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been rep

Dosage and Administration

INFECTION*	ADULTS	CHILDREN
		Dosage should not in a dose higher tha for adults.
Respiratory Tract		
Tonsillitis & Pharyngitis**	250 mg q.i.d. in equally spaced doses	body weight <20 k lbs) 125 mg q.i.d equally spaced dose body weight >20 k lbs) 250 mg q.i.d equally spaced dose
Bronchitis and Pneumonia		
Mild or Moderate Infections	250 mg q.i.d. in equally spaced doses	50 mg/kg/day q.i. equally spaced dose
Chronic Infections	500 mg q.i.d. in equally spaced doses	100 mg/kg/day q.i. equally spaced dose
Otitis Media	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/kg/d equally spaced dose pending on severity
Skin & Skin Structures	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/kg/d equally spaced dose pending on severity
Urinary Tract	500 mg q.i.d. in equally spaced doses	100 mg/kg/day in eq spaced doses.

*As with antibiotic therapy generally, treatment should be continued minimum of 48 to 72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.

**In infections caused by Group A beta-hemolytic streptococci, a minimu 10 days of treatment is recommended to guard against the risk of rheur fever or glomerulonephritis.

In the treatment of chronic urinary tract infection, frequent bacteriologic clinical appraisal is necessary during therapy and may be required for se months afterwards.

Persistent infection may require treatment for several weeks.

Cyclacillin is not indicated in children under 2 months of age.

Patients with Renal Failure

Based on a dosage of 500 mg q.i.d., the following adjustment in do interval is recommended:

Patients with a creatinine clearance of >50 ml/min need no age interval adjustment.

Patients with a creatinine clearance of 30-50 ml/min should receive doses every 12 hours.

Patients with a creatinine clearance of between 15-30 ml/min sh receive full doses every 18 hours.

Patients with a creatinine clearance of between 10-15 ml/min sh receive full doses every 24 hours.

In patients with a creatinine clearance of < 10 ml/min serum creatinine values of ≥ 10 mg %, serum cyclacillin levels are rec mended to determine both subsequent dosage and frequency.

Wyeth Laboratories
Philadelphia, Pa. 19101

Partial Resolution of Bone Lesions

A Child With Severe Combined Immunodeficiency Disease and Adenosine Deaminase Deficiency After Enzyme-Replacement Therapy

Barry S. Yulish, MD; Robert C. Stern, MD; Stephen H. Polmar, PhD, MD

• A child with severe combined immunodeficiency disease and adenosine deaminase deficiency, with characteristic bone dysplasia, was treated with transfusions of frozen irradiated RBCs as a means of enzyme replacement. This therapy resulted in restoration of immunologic competence and partial resolution of the bone lesions. Although the natural history of these lesions without therapy is not known, enzyme-replacement therapy may have played a role in the resolution of this patient's bone lesions.

(*Am J Dis Child* 134:61-63, 1980)

Adenosine deaminase (ADA) deficiency is associated with an autosomal recessive form of severe combined immunodeficiency disease (SCID).[1] In addition to immunodeficiency, a characteristic bone dysplasia has been observed in many children with this condition.[2,3] Bone dysplasias similar to those of ADA-deficient patients with SCID have also been reported for various syndromes associated with immunologic incompetence.[4-8] However, the ADA status of these patients was not reported. Roentgenographic features of the bone dysplasia in patients with ADA deficiency include broad, flared, and cupped anterior ends of ribs, and pelvic abnormalities that include flat, irregular acetabular roofs, decreased vertical height of the innominate bones, and narrow sacrosciatic notches.[2] Mild platyspondylia and increased height of intervertebral disk spaces as well as cupping of the posterior rib ends are less prominent findings.[2] Children with SCID have an absence of both cell-mediated and humoral immunity and, if untreated, usually die of infection before age 2 years. Bone marrow transplantations from histoidentical donors have resulted in immunologic reconstitution in some patients.[9] We have treated a child with SCID associated with ADA deficiency with repeated transfusions of frozen irradiated RBCs as a source of ADA.[10] This form of enzyme-

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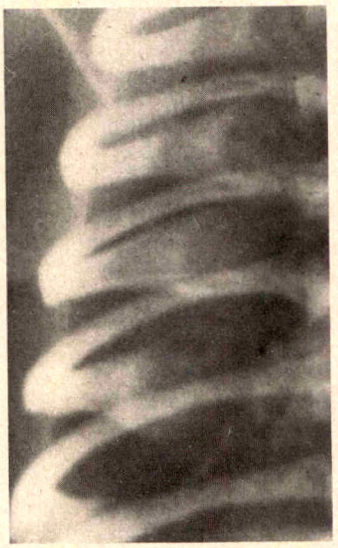

Fig 1.—Ribs shortly after birth. Note cupping of anterior rib ends.

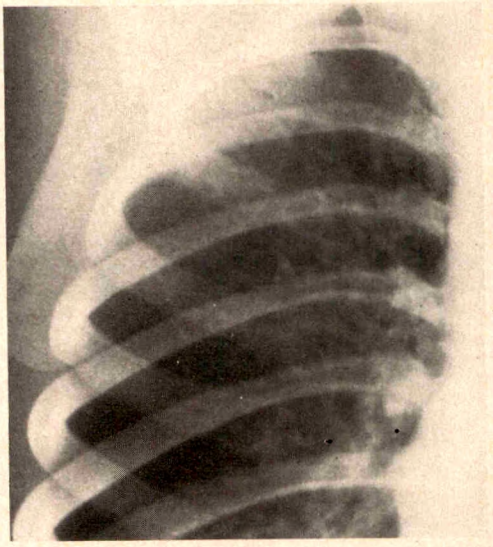

Fig 2.—Ribs at age 2 years. No cupping of rib ends is present.

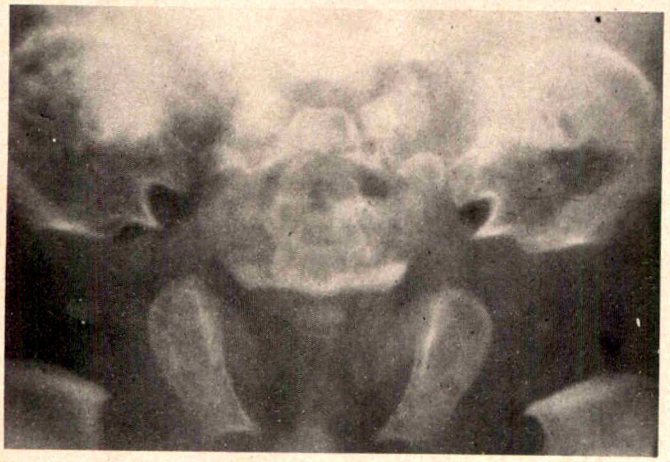

Fig 3.—Pelvis at age 3 months. Note short vertical height of iliac bones, flat acetabular roofs, short sacrosciatic notches, and wide ischia.

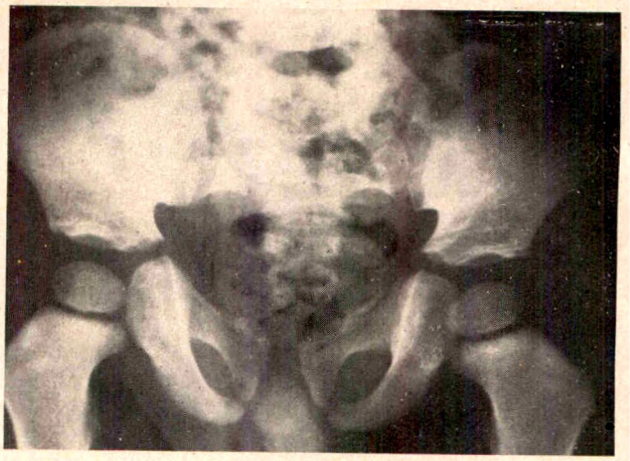

Fig 4.—Pelvis at age 2 years. Acetabular roofs are not as flat, sacrosciatic notches are not as narrow, but ischia are still widened.

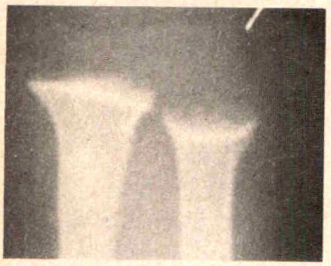

Fig 5.—Wrist at age 3 months. Metaphyses are broad, cupped, and flared.

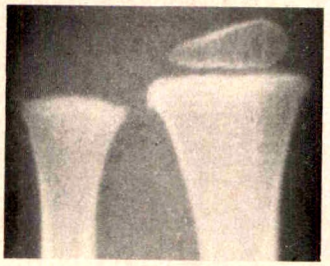

Fig 6.—Wrist at age 2 years. Note normal appearance of metaphyses.

Fig 7.—Normal bony pelvis of infant for comparison.

replacement therapy restored both humoral and cell-mediated immunity. Roentgenograms of the chest on the day of birth and of the chest and bones up to age 7 months demonstrated characteristic bone lesions as well as flaring and cupping of some long-bone metaphyses. Treatment was begun at 7 months of age and, after 17 months of therapy with intermittent transfusions of RBCs, roentgenograms made at age 2 years demonstrate great resolution of bone lesions.

REPORT OF A CASE

Adenosine deaminase deficiency was diagnosed prenatally by measurement of ADA activity in cultures of amniotic cells after amniocentesis.[11] The patient was transferred to Rainbow Babies and Childrens Hospital, Cleveland, at 1 day of age and placed in protective isolation, which was maintained until one week prior to discharge from the hospital at 12 months of age. The diagnosis of SCID was confirmed by studies of in vitro lymphocyte responses and immunologic evaluation. In vitro studies demonstrated that exogenous ADA restored normal lymphocyte-proliferative responses to mitogens.[12] These studies suggested that in vivo administration of ADA might improve the immunologic function of the patient. Blood transfusion is usually contraindicated in SCID because of the risk of graft vs host disease. However, frozen irradiated RBCs, which are free of viable lymphocytes, were found to be a safe source of encapsulated human ADA.[10] At age 7 months, the child received the first of several transfusions of frozen irradiated RBCs. This therapy resulted in the restoration of both humoral and cell-mediated immunity.[10] He was subsequently discharged home and has been readmitted for transfusion of frozen irradiated RBCs at four- to six-week intervals. He has remained free of clinically apparent infection throughout his course of treatment, except for three urinary tract infections and a perianal abscess prior to the beginning of therapy. His height and weight have followed the tenth-percentile line.

RESULTS

Rib abnormalities were present on a roentgenogram made at birth (Fig 1) but not on one made at age 2 years (Fig 2), after 17 months of ADA-replacement therapy. Pelvic abnormalities present at age 3 months (Fig 3), have regressed at age 2 years (Fig 4), with increased size of the sacrosciatic notches and more slope to the acetabular roofs. Some pelvic abnormalities persist, however, including broad ischia.

Wrist roentgenograms made at age 3 months (Fig 5) show broad, cupped, and flared metaphyses, but those made at age 2 years (Fig 6) show no abnormalities.

Figure 7 shows a normal bony pelvis of an infant for comparison.

COMMENT

The bone dysplasia demonstrated in our patient shortly after birth has many features characteristic of ADA deficiency-SCID.[2] Similar bone dysplasias have been reported in other immunologically deficient patients,[4-8] but the ADA status of these patients is unknown. The rib abnormalities alone are not specific, but may also be seen in patients with SCID and normal RBC ADA.[2]

The natural history of the bone lesion is unknown, although histologic study of the costochondral junctions and vertebrae by Cederbaum et al[13] showed absence of the zone of proliferative cells, lack of organized cartilage-cell columns, uninterrupted formation of calcified cartilage, and lack of trabecular formation. It is possible that the dysplasia could regress with advancing age even in the absence of any treatment, but few patients whose conditions were untreated have survived beyond 2 years of age. Bone lesions have recently been reported to improve after bone marrow transplantation; however, this procedure results in metabolic changes similar to those observed in patients treated by RBC enzyme-replacement therapy.[14] Thus, bone marrow transplantation interferes with the natural history of the metabolic disturbance in ADA deficiency and these patients cannot serve as controls for the patients whose conditions were treated with RBC transfusions.

Patients with ADA deficiency have been found to have elevated levels of adenosine triphosphate (ATP), deoxy-ATP, and cyclic adenosine-3′, 5′-monophosphate (cAMP) in their lymphocytes.[10,15,16] We have hypothesized that the mechanism by which transfusion restores immunocompetence is that the RBC ADA catabolizes adenosine or deoxyadenosine that diffuses out of the lymphocytes and into the RBCs.[10] This reduces the lymphocyte adenosine (or deoxyadenosine) levels and eliminates the accumulation of excess ATP, deoxy-ATP, and cAMP. It is tempting to speculate that a similar metabolic defect is operative in osteoblasts or chondroblasts (ie, that intracellular levels of adenosine and cAMP are excessive and that the RBC ADA catabolizes adenosine that diffuses out of the osteoblasts or chondroblasts). Further observation on the course of the bone defect in patients with untreated ADA deficiency as well as in those whose conditions are treated with intermittent RBC transfusions or bone marrow transplants will help elucidate the pathophysiology of the bone defect and could provide new insight concerning normal bone growth.

References

1. Giblett ER, Anderson JE, Cohen F, et al: Adenosine deaminase deficiency in two patients with severely impaired cellular immunity. *Lancet* 2:1067-1069, 1972.
2. Meuwissen HJ, Pollara B, Pickering RJ: Combined immunodeficiency disease associated with adenosine deaminase deficiency. *J Pediatr* 86:169-181, 1975.
3. Yount J, Nichols P, Ochs H, et al: Absence of erythrocyte adenosine deaminase associated with severe combined immunodeficiency. *J Pediatr* 84:173-177, 1974.
4. Alexander WJ, Dunbar JS: Unusual bone changes in thymic alymphoplasia. *Ann Radiol* 11:389-394, 1968.
5. Say B, Tinaztepe B, Tinaztepe K, et al: Thymic dysplasia associated with dyschondroplasia in an infant. *Am J Dis Child* 123:240-244, 1972.
6. Gatti R, Platt N, Pomerance HH, et al: Hereditary lymphopenic agammaglobulinemia associated with a distinctive form of shortlimbed dwarfism and ectodermal dysplasia. *J Pediatr* 75:675-684, 1969.
7. McKusick V, Cross H: Ataxia-telangiectasia and Swiss-type agammaglobulinemia. *JAMA* 195:739-745, 1966.
8. Clinicopathological conference: A case of Swiss-type agammaglobulinemia and achondroplasia. *Br Med J* 2:1371-1373, 1966.
9. Parkman R, Gelfand EW, Rosen FS, et al: Severe combined immunodeficiency and adenosine deaminase deficiency. *N Engl J Med* 292:714-719, 1975.
10. Polmar SH, Stern RC, Schwartz AL, et al: Enzyme replacement therapy for adenosine deaminase deficiency and severe combined immunodeficiency. *N Engl J Med* 295:1337-1343, 1976.
11. Hirschhorn R, Beratis N, Rosen FS, et al: Adenosine deaminase deficiency in a child diagnosed prenatally. *Lancet* 1:73-75, 1975.
12. Polmar SH, Wetzler EM, Stern RC, et al: Restoration of *in vitro* lymphocyte responses with exogenous adenosine deaminase in a patient with severe combined immunodeficiency. *Lancet* 2:743-746, 1975.
13. Cederbaum SD, Kaitila I, Rimoin DL, et al: The chondroosseous dysplasia of adenosine deaminase deficiency with severe combined immunodeficiency. *J Pediatr* 89:737-742, 1976.
14. Ochs H: Immune reconstitution after bone marrow transplantation and studies of purine metabolism in a patient with ADA deficiency, in Pollara B, Meuwissen HJ, Porter IH (eds): *Inborn Errors of Specific Immunity* (Birth Defects Symposium IX). New York, Academic Press Inc, in press.
15. Cohen A, Hirschhorn R, Horowitz SD, et al: Deoxyadenosine triphosphate as a toxic metabolite in adenosine deaminase deficiency. *Proc Natl Acad Sci USA* 75:472-476, 1978.
16. Schmalsteig FC, Nelson JA, Mills GC, et al: Increased purine nucleotides in adenosine deaminase deficient lymphocyte. *J Pediatr* 91:48-51, 1977.

Metabolic Studies in a Child With a Pancreatic Insulinoma

Fredda Ginsberg-Fellner, MD, Elliot J. Rayfield, MD

• **An 8-year-old boy with a convulsive disorder for 3½ years remained seizure free for 20 months while being treated with phenytoin (diphenylhydantoin) sodium, and then he had a relapse. He first demonstrated hypoglycemia when he fasted prior to being placed on a ketogenic diet. An oral glucose tolerance test indicated fasting and postglucose hypoglycemia and substantial hyperinsulinemia. Somatostatin infusion resulted in a modest increase in plasma glucose levels and a decrease in serum insulin concentrations. A discrete pancreatic mass was demonstrated preoperatively by celiac angiography that on surgical extirpation, proved to be a benign intrapancreatic insulinoma. Evaluation for islet cell tumors is of importance in children with seizure disorders unresponsive to anticonvulsant medication. Furthermore, somatostatin may be useful preoperatively in maintaining normal blood glucose concentrations in patients with islet cell adenomas.**

(*Am J Dis Child* 134:64-67, 1980)

Pancreatic islet cell adenomas are uncommon in childhood. Zuppinger[1] summarized 48 cases, whereas Cornblath and Schwartz[2] indicated that 88 cases have been described. All authors agreed that most children had neurologic symptoms, convulsions being the most prominent.[3,4] The use of phenytoin (diphenylhydantoin) sodium in such children has rarely been commented on although this agent is often used as an anticonvulsant and is known to inhibit insulin secretion. Recently, we studied an 8-year-old child who had been treated with phenytoin for 3½ years and who subsequently was found to have a benign pancreatic insulinoma. During the period prior to surgery, maintenance of normal blood glucose levels in our patient was difficult. Therefore, somatostatin, a tetradecapeptide hormone widely distributed in the CNS, gastrointestinal tract, and delta cells of the islets of Langerhans[5-8] and a known inhibitor of insulin, glucagon, and growth hormone secretion,[9-12] was used in an effort to increase the patient's blood glucose concentrations. We report the results of metabolic studies in this patient after fasting, oral dextrose administration, and somatostatin infusion.

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REPORT OF A CASE

An 8-year-old boy was admitted to Mount Sinai Medical Center with a three-year history of recurring seizures. At age 4½ years, he first had several nocturnal screaming episodes. An EEG was abnormal, and treatment with phenytoin resulted in complete remission of these symptoms for 20 months. Recurrent episodes of weakness and flaccidity followed by hunger for sugar-laden cereals ensued and were not relieved by increases in the dose of phenytoin. Ten months prior to the present hospitalization, the EEG and results of CSF and neurological examinations were all normal; a fasting plasma glucose level was 70 mg/dL, and a two-hour postprandial value was 78 mg/dL. Eight months later, the EEG, computerized axial tomography, skull roentgenograms, and results of serum magnesium, calcium, toxicology, plasma amino acids, and three fasting blood glucose tests were all normal.

Despite the fact that carbamazepine (Tegretol) and primidone (Mysoline) were added to the anticonvulsant therapy, the seizures increased in frequency, and the patient was readmitted to the hospital for institution of a ketogenic diet. He was an obese, highly irritable child. His height was 118 cm (< third percentile for age); weight, 24.5 kg (50th percentile for age and height); and head circumference, 53 cm. An EEG then showed severe cerebral dysfunction. Serum thyroxine, triiodothyronine, and thyroid-stimulating hormone by radioimmunoassay, urinary vanillylmandelic acid and urinary free cortisol levels were all within normal limits. Bone age was 7 years and 8 months. The patient was begun on a diagnostic fast, and within two hours, he had generalized seizures develop. The plasma glucose level was then 25 mg/dL, the serum insulin level was 96 μU/mL and the glucose-insulin ratio was 0.26 (adult normal, ≥6[13]; normal range for children in our laboratory, 8 to 15). Phenytoin therapy was

then discontinued. One day later, an oral glucose tolerance test was performed; dextrose, 1.75 g/kg, as a 50% solution (43 g) was administered. Ten days later, a somatostatin infusion was started; 330 μg of somatostatin was given during a 40-minute period, followed by 500 μg during the next 30 minutes. This latter test was performed to determine the feasibility of inhibiting exaggerated insulin release preoperatively; when maintenance of normal plasma glucose concentrations can be extremely difficult. Celiac and superior mesenteric angiograms showed a discrete 1- to 2-cm lesion in the midportion of the pancreas. Liver scan was normal.

For the 11 days prior to surgery, plasma glucose levels were maintained between 50 and 80 mg/dL by the use of a 1,600-calorie diet (60% carbohydrate, 15% protein, 25% fat) divided into six to eight meals and of a 10% dextrose solution, intravenously, that provided dextrose at 0.28 g/kg/hr. At surgery, a 1.5-cm well-encapsulated intrapancreatic mass was identified immediately superior to the junction of the superior mesenteric and inferior pancreatic arteries and was then excised. No other masses were found. The pathologic picture was that of a typical insulinoma, with tumor cells, on light microscopic examination, forming both islet and ribbon-like structures. On ultrastructural studies, there were cytoplasmic granules typical of those normally seen in beta cells of the islets of Langerhans. No other cell types were identified. Microscopic sections of the pancreas, not involved by tumor, were completely normal. During surgery, plasma glucose values peaked at 350 mg/dL immediately after removal of the tumor, whereas the serum insulin level decreased from 35 to 16 μU/mL 14 minutes after tumor removal and to 9 μU/mL 46 minutes later. Postoperatively, serum amylase levels peaked at 220 units and the plasma glucose level gradually decreased from 285 mg/dL to 88 mg/dL by the seventh day. Glycosuria was present until the third postoperative day. The patient has remained asymptomatic during the past 24 months, with fasting glucose values ranging from 70 to 84 mg/dL and serum insulin levels ranging from 6 to 10 μU/mL.

MATERIALS AND METHODS

Plasma glucose was measured by the glucose-oxidase method with an automated system of chemical analysis. Serum immunoreactive insulin (IRI), growth hormone,[14] proinsulin,[15] and plasma glucagon,[16] were measured by radioimmunoassay procedures. The glucagon assay was performed using 30K glucagon antiserum purchased from Roger Unger, MD. Informed consent was obtained for all studies from the patients' parents. Permission for use of the somatostatin (Emergency IND No. 12460, Federal Drug Administration, Edwin Ortiz) was obtained. The somatostatin was obtained from Roger Guillemin, MD, PhD, at the Salk Institute, San Diego, in the form of dihydrosomatostatin as synthesized by Jean Rivier. It was dissolved in physiologic sodium chloride solution (0.5 mg/mL) and filtered through a 0.22-μ filter (Millipore) into 2-mL unit dose, pyrogen-free vials, with a concentration of 1 mg/mL. It was then further diluted in physiologic saline solution just prior to use at a final concentration of 20 μg/mL and was administered by an infusion pump.

RESULTS

Glucose Tolerance Test

The results of the glucose tolerance test are depicted in Fig 1. Fasting and postglucose hypoglycemia are noted. The fasting glucose level was 34 mg/dL and a nadir of 20 mg/dL was reached two hours after dextrose ingestion. This was accompanied by notable hyperinsulinemia at all test points, with a peak value of 334 μU/mL at 15 minutes (normal, 50 μU/mL) and a value of 144 μU/mL when blood glucose reached its lowest level at the two-hour point. Fasting hyperinsulinemia (50 μU/mL; normal, 2 to 20 μU/mL) was also present. As shown in Fig 1, the fasting proinsulin level of 9.5% was within the normal range (normal, 5% to 22%); at two hours, however, the value rose to 23.6%.

Somatostatin Infusion

The results of the somatostatin infusion are shown in Fig 2. Plasma glucose levels gradually increased, beginning 20 minutes after the start of the somatostatin infusion. The 38% increase from 47 to 65 mg/dL occurred gradually during the final 50 minutes of the study period; it was greatest between 20 and 30 minutes, at the time the lower somatostatin dosage was being infused. Plasma glucagon levels (75 to 95 pg/mL) were within the normal range in our laboratory (50 to 120 pg/mL; with normal children's values in the higher limit) and did not change substantially during the infusion. Serum growth hormone declined by 50% during the first 20 minutes of the study. This was followed by a paradoxical increase to 7.4 ng/mL 30 minutes after the start of the somatostatin infusion. Thereafter, growth hormone levels declined steadily for the remainder of the study.

COMMENT

Islet cell tumors are rare during childhood, with convulsions and behavioral changes being prominent in both the pediatric and adult age groups. In adults, delay in diagnosis has been reported to be associated with administration of phenytoin. Thus, a 44-year-old man described by Knopp et al[17] had convulsions for 17 years; withdrawal of the anticonvulsant resulted in an increase in insulin levels from 20 to 41 μU/mL. In children, prior administration of phenytoin was only documented in three cases, and there were no comments as to how drug administration affected the patient's clinical course or metabolic evaluation.[18-20] Our patient initially had a therapeutic response to phenytoin for 20 months. However, convulsive episodes recurred, and he experienced fasting hypoglycemia and an exaggerated insulin response to oral dextrose administration. The blunting effect on insulin secretion by phenytoin has been documented in adults with islet cell tumors,[21] normal children and adults,[22,23] laboratory animals,[24] and in vivo islet cell systems.[25] Also note that fasting proinsulin levels were not elevated in our patient, in contrast to the situation usually described in adults.[15] The normal proinsulin levels, too, could be an effect of phenytoin administration.

Similar reduction in beta cell tumor insulin release has recently been reported after the administration of somatostatin. Thus, Scuro et al[26] reported that somatostatin infusions produced slight decreases in basal insulin levels and inhibition of glucose-, glucagon-, and tolbutamide sodium-induced insulin release in two women, one of whom had a documented pancreatic insulinoma. Curnow and co-workers[27] showed that somatostatin suppressed elevated insulin levels in a 54-year-old woman with metastatic pancreatic islet cell carcinoma. Similar suppression was

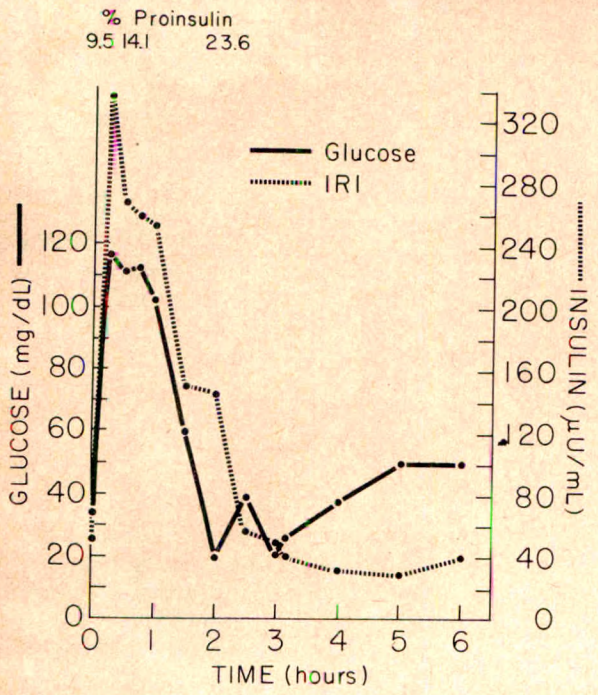

Fig 1.—Oral glucose tolerance test. IRI indicates immunoreactive insulin. Percent proinsulin concentrations (of total IRI) are indicated at 0, one half, and two hours.

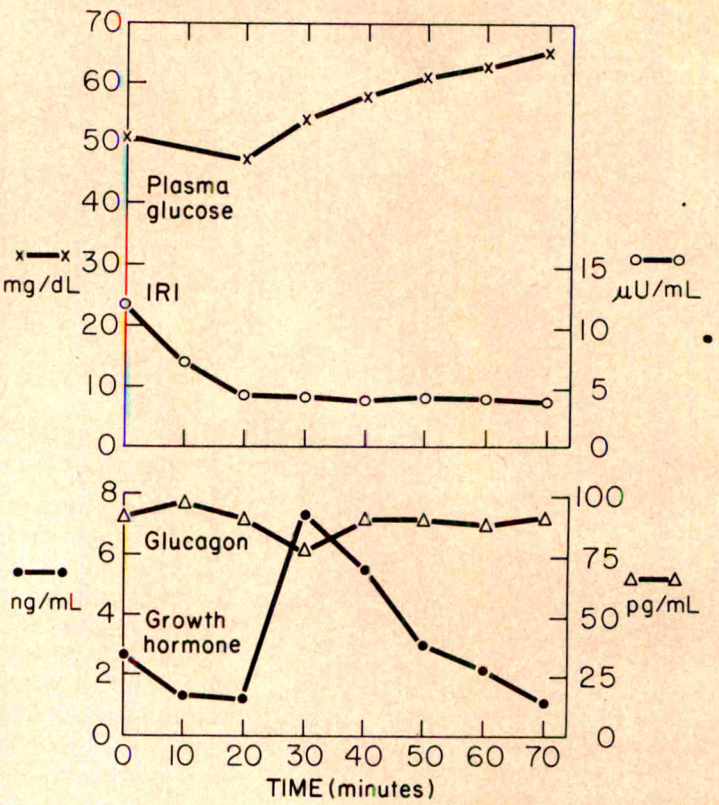

Fig 2.—Somatostatin infusion study. Plasma glucose concentrations and serum immunoreactive insulin (IRI) concentrations are shown in upper panel. Plasma immunoreactive glucagon concentrations and serum growth hormone concentrations are depicted in lower panel.

more recently reported in an infant with nesidioblastosis.[28] In that child, administration of synthetic cyclic somatostatin at a rate of 120 μg/hr (or 20 μg/kg/hr) resulted in a decrease of serum IRI from 6.8 to 2 μU/mL within 20 minutes after the start of the somatostatin infusion. The rise in the blood glucose level, however, did not occur until one hour after the serum insulin level began to fall. In our patient, the somatostatin's suppression of insulin and the increase in the plasma glucose level both commenced at the same time, within ten minutes of the beginning of the starting, lower-dosage (20.2 μg/kg/hr) somatostatin infusion. In addition, the increase in the plasma glucose level continued throughout the time of infusion, whereas the serum insulin level fell to its nadir of 4 μU/mL 20 minutes after the start of the somatostatin administration and did not decrease further despite the 100% increase in the dosage of the somatostatin to 40.8 μg/kg/hr.

Therefore, similar somatostatin dosages (20 μg/kg/hr) in both our patient with an insulinoma and in the infant with nesidioblastosis[28] produced similar patterns of depression of serum IRI concentrations. The lag in resultant increases in plasma glucose concentrations in the child with nesidioblastosis may reflect the different pathologic picture of the two disease entities or may result from the nature of the different types of somatostatin used in the two studies.

Thus, the insulin-producing cells in both our patient and in the infant with nesidioblastosis showed increased sensitivity to somatostatin that was reflected by slowly increasing blood glucose concentrations. Glucagon levels, however, were not suppressed, which is also similar to the results reported in the infant with nesidioblastosis. Although the glucagon levels in our patient were inappropriately low in the presence of hypoglycemia, comparably low fasting glucagon levels have recently been reported in 12 patients with solitary islet cell adenomas.[29] In these latter subjects, whose ages ranged from 15 to 68 years, plasma immunoreactive glucagon concentrations ranged from 42 to 141 pg/mL, with a mean of 96 pg/mL. These data suggest some derangement in the regulation of glucagon secretion by glucose in such patients as well as a decreased sensitivity to somatostatin-induced inhibition of glucagon release.

The paradoxical rise in growth hormone in our patient during somatostatin infusion was also seen in the infant with nesidioblastosis under similar circumstances. In both children, however, growth hormone levels decreased after this paradoxical rise. The reasons for this temporary "escape" in growth hormone suppressibility by somatostatin remain to be elucidated.

It is apparent from our experience and a review of the literature that all children with unremitting seizure disorders should have fasting blood glucose and simultaneous serum insulin determinations performed to identify possible pancreatic islet cell tumors. Furthermore, physicians

should be aware that phenytoin may initially obscure the diagnosis of insulinoma. Thus, stimulation and suppression tests, including oral glucose tolerance, tolbutamide stimulation, and fasts with sequential insulin determinations, may be required after phenytoin therapy has been discontinued. Finally, somatostatin may be useful in reducing insulin secretion in the preoperative period when maintenance of normal blood glucose concentrations may be extremely difficult.

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Charles Brill, MD, referred this patient. Erica Sapira provided excellent technical assistance. Arthur Rubenstein, MD, measured the serum proinsulin levels. The Arnel Co, Brooklyn, NY, supplied rabbit anti-guinea pig serum.

Nonproprietary Name and Trademark of Drug

Tolbutamide sodium—*Orinase Diagnostic.*

References

1. Zuppinger KA: Hypoglycemia caused by increased peripheral glucose utilization: A. B-cell adenoma, in Falkner F, Kretchmer N, Rossi E (ed): *Hypoglycemia in Childhood: Evaluation of Diagnostic Procedures.* Basel, Switzerland, S Karger, 1975, pp 23-26.

2. Cornblath M, Schwartz R: Islet cell adenoma in childhood, in Schaffer AJ (ed): *Disorders of Carbohydrate Metabolism in Infancy,* ed 2. Philadelphia, WB Saunders Co, 1976, pp 382-392.

3. Service FJ, Dale AJD, Elveback LR, et al: Insulinoma: Clinical and diagnostic features in 60 consecutive cases. *Mayo Clin Proc* 51:417-429, 1976.

4. Boley SJ, Lin J, Schiffman A: Functioning pancreatic adenomas in infants and children. *Surgery* 48:592-605, 1960.

5. Hokfelt T, Efendic S, Hellerstrom C, et al: Cellular localization of somatostatin in endocrine-like cells and neurons of the rat with special references to the A_1-cells of the pancreatic islets and to the hypothalamus. *Acta Endocrinol* 200(suppl):5-41, 1975.

6. Dubois MP: Immunoreactive somatostatin is present in discrete cells of endocrine pancreas. *Proc Natl Acad Sci USA* 72:1340-1343, 1975.

7. Arimura A, Soto H, Dupont A, et al: Somatostatin: Abundance of immunoreactive hormone in rat stomach and pancreas. *Science* 189:1007-1009, 1975.

8. Orci L, Unger RH: Functional subdivision of islets of Langerhans and possible role of D cells. *Lancet* 2:1243-1244, 1975.

9. Alberti KGMM, Christensen NG, Christensen SE, et al: Inhibition of insulin secretion by somatostatin. *Lancet* 2:1299-1301, 1973.

10. DeVane GW, Siler TM, Yen SSC: Acute suppression of insulin and glucose levels by synthetic somatostatin in normal human subjects. *J Clin Endocrinol Metab* 38:913-915, 1974.

11. Mortimer CH, Tunbridge WMG, Carr D, et al: Effects of growth hormone release-inhibiting hormone on circulating glucagon, insulin, and growth hormone in normal, diabetic, acromegalic, and hypopituitary patients. *Lancet* 1:697-701, 1974.

12. Gerich JE, Lorenzi M, Schneider V, et al: Inhibition of pancreatic glucagon responses to arginine by somatostatin in normal man and in insulin-dependent diabetics. *Diabetes* 23:876-880, 1974.

13. Turner RC, Oakley NW, Nabarro JDN: Control of basal insulin secretion, with special reference to the diagnosis of insulinomas. *Br Med J* 2:132-135, 1971.

14. Juan C, AvRuskin TW: A combined immunoassay of human growth hormone and insulin: Cumulative assessment of assay performance. *J Clin Endocrinol Metab* 33:150-152, 1971.

15. Melani F, Rubenstein AH, Steiner DF: Human serum proinsulin. *J Clin Invest* 49:497-507, 1970.

16. Aguilar-Parada E, Eisentraut AM, Unger RH: Pancreatic glucagon secretion in normal and diabetic subjects. *Am J Med Sci* 257:415-419, 1969.

17. Knopp RH, Sheinin JC, Freinkel N: Diphenylhydantoin and an insulin-secreting islet adenoma. *Arch Intern Med* 130:904-908, 1972.

18. Mann JR, Rayner PHW, Gourevitch A: Insulinoma in childhood. *Arch Dis Child* 44:435-442, 1969.

19. Zweibel PC: Insulinoma: Review of seven cases at the Mount Sinai Hospital in light of current literature. *Mt Sinai J Med NY* 43:637-656, 1976.

20. Hartmann AF Sr, Wohltmann HJ, Holowach J, et al: Studies in hypoglycemia. *J Pediatr* 56:211-233, 1960.

21. Hofeldt FD, Dippe SE, Levin SR, et al: Effects of diphenylhydantoin upon glucose-induced insulin secretion in three patients with insulinoma. *Diabetes* 23:192-198, 1974.

22. Peters BH, Samaan NA: Hyperglycemia with relative hypoinsulinemia in diphenylhydantoin toxicity. *N Engl J Med* 281:91-92, 1969.

23. Treasure T, Toseland PA: Hyperglycaemia due to phenytoin toxicity. *Arch Dis Child* 46:563-564, 1971.

24. Belton NR, Etheridge JE Jr, Millichap JG: Effect of convulsions and anti-convulsants on blood sugar in rabbits. *Epilepsia* 6:243-249, 1965.

25. Levin SR, Grodsky GM, Hagura R, et al: Comparison of the inhibitory effects of diphenylhydantoin and diazoxide upon insulin secretion from the isolated perfused pancreas. *Diabetes* 21:856-862, 1972.

26. Scuro LA, Locascio V, Adami S, et al: Somatostatin inhibition of insulin secretion in insulin-producing tumors. *Metabolism* 25:603-609, 1976.

27. Curnow RT, Carey RM, Taylor A, et al: Somatostatin inhibition of insulin and gastrin hypersecretion in pancreatic islet-cell carcinoma. *N Engl J Med* 292:1385-1386, 1975.

28. Hirsch HJ, Loo S, Evans N, et al: Hypoglycemia of infancy and nesidioblastosis: Studies with somatostatin. *N Engl J Med* 296:1323-1326, 1977.

29. Cloutier MG, Pek S, Crouther RL, et al: Glucagon-insulin interactions in patients with insulin-producing pancreatic islet lesions. *J Clin Endocrinol Metab* 48:201-206, 1979.

Foreign Body in the Airway

A Review of 200 Cases

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• **Two hundred children aged 6 months to 12 years were admitted to the hospital with a foreign body in the airway. Food materials constituted 93% of all foreign bodies. A positive history of foreign body aspiration was obtained in 88% of the cases. The most common symptoms of laryngotracheal foreign bodies were dyspnea, cough, and stridor, whereas those of bronchial foreign bodies were cough, decreased air entry, wheezing, and dyspnea. Chest fluoroscopy contributed to the diagnosis in 90% of the cases of bronchial foreign bodies, but only 32% of those in the laryngotracheal area. Of the foreign bodies removed, 98½% were done by laryngoscopy, tracheoscopy, and/or bronchoscopy. Complications were involved in 6% of the cases, including one death. History of recurrent intractable pneumonia should make one consider a foreign body in the airway. Removal of one foreign body does not exclude the existence of another. The condition may be fatal; thus immediate removal of the foreign body is mandatory.**

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The presence of a foreign body in the respiratory tract is a serious and, on occasion, fatal condition.[1,2] Early diagnosis and removal of the inhaled material may save the patient chronic illness, an existence as an invalid, or possibly death. Despite the great progress in the methods of endoscopy and anesthesia, great difficulties and complications are still present owing to limitations of diagnostic procedures. This report highlights the particular clinical and roentgenographic features and problems of laryngotracheal and bronchial obstruction after the inhalation of foreign bodies by 200 infants and children.

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SUBJECTS AND METHODS

In the course of 12 years, from 1966 to 1977 inclusive, 200 cases of airway obstruction owing to foreign bodies were treated in the pediatric departments, Rambam Medical Center, Haifa, Israel. We reviewed the records of those patients, noting the age and sex of each patient and the time lag between the aspiration or onset of symptoms and hospitalization. In 193 infants and children, chest roentgenograms that included inspiratory and expiratory anteroposterior and lateral films were performed, and in 192 children, fluoroscopy was performed, and the correlation between them and the endoscopic results was noted.

This review includes 197 cases in which the presence of foreign bodies in the respiratory tracts was proved by laryngoscopy, tracheoscopy, and/or bronchoscopy, one case by thoracotomy, and two cases by the coughing out of the aspirated foreign body.

RESULTS

Approximately 85% of the patients studied were less than 3 years of age, and the youngest patient was 6 months old (Table 1). The male-female ratio was about 2:1.

Only 54% of the children were referred to the hospital within three days of aspiration or onset of symptoms and signs, whereas 18% of the children were sent to the hospital after more than one month, either because their parents failed to seek medical attention for their child or because the physician did not realize the true cause of the symptoms (Table 2). In most cases (88%), the children were known to have aspirated something. Table 3 gives the incidence of initial symptoms and signs according to the site of lodgment of foreign bodies.

The most common roentgenographic finding in those patients with bronchial foreign bodies was obstructive emphysema. More than one half of the children with laryngotracheal foreign bodies had normal chest roentgenograms (Table 4). The most common fluoroscopic finding in those patients with bronchial foreign bodies was inspiratory shift of mediastinal shadow, and normal fluoroscopic findings were the most common in those patients with laryngotracheal foreign bodies (Table 5).

Of all the foreign bodies, 76% were lodged in the main bronchi, and 17% were lodged in the larynx or trachea (Table 6). Most foreign bodies were organic (93%), and almost half of all foreign bodies were peanuts (Table 7). All children less than 1 year of age aspirated organic foreign bodies.

The most common complication of foreign body aspiration was pneumonia (22%). Atelectasis was seen in 10% of the cases, bronchiectasis in 1%, and pneumothorax in 0.5%.

Table 1.—Age Distribution for Foreign Body Aspiration

	Cases (N = 200)
Age, yr	No. (%)
0-1	21 (10.5)
1-2	102 (51)
2-3	48 (24)
3-4	10 (5)
> 4	19 (9.5)

Table 2.—Time Lapse From Aspiration* to Hospitalization

	Cases (N = 200)
No. of Days	No. (%)
0-1	68 (34)
2-3	41 (20.5)
4-7	24 (12)
8-30	29 (14.5)
31-90	30 (15)
> 90	7 (3.5)
No record	1 (0.5)

*Or onset of symptoms.

Table 3.—Incidence of Symptoms and Signs by Lodgment Site of Foreign Bodies*

	Site	
	Bronchial (N = 163)	Laryngotracheal (N = 35)
Symptoms and Signs	No. (%)	No. (%)
Cough	154 (94.5)	23 (65.7)
Decreased air entry	100 (61.3)	7 (20)
Wheezing	97 (59.5)	9 (25.7)
Dyspnea	96 (58.9)	26 (74.3)
Fever	59 (36.2)	1 (2.9)
Cyanosis	55 (33.7)	14 (40)
Rales	52 (31.9)	9 (25.7)
Stridor	21 (12.9)	22 (62.9)
Recurrent pneumonia	7 (4.3)	.....
Rhonchi	3 (1.8)	.....
Hoarseness	2 (1.2)	4 (11.4)
Chest pain	1 (0.6)	.....
Recurrent respiratory tract infection	1 (0.6)	1 (2.9)
Fetor	1 (0.6)	.....
Coma, cardiac arrest	2 (1.2)	.....
Asymptomatic	2 (1.2)	.....

*More than one of these findings are present in some cases.

Table 4.—Roentgenographic Findings*

	Site (N = 193)	
	Bronchial (N = 160)	Laryngotracheal (N = 33)
Findings	No. (%)	No. (%)
Obstructive emphysema	99 (61.9)	5 (15.6)
Pneumonia	28 (17.5)	6 (18.2)
Normal	25 (15.6)	20 (60.6)
Atelectasis	20 (12.5)	.....
Radiopaque foreign body	6 (3.8)	2 (6)
Pneumothorax	1 (0.6)	.....
Bronchiectasis	1 (0.6)	.....

*More than one of these findings are present in some cases.

Table 5.—Chest Fluoroscopic Findings

	Site (N = 192)	
	Bronchial (N = 161)	Laryngotracheal (N = 31)
Findings	No. (%)	No. (%)
Inspiratory shift of mediastinal shadow	145 (90.1)	4 (12.9)
Inspiratory widening of mediastinal shadow	7 (4.3)	10 (32.3)
Normal	7 (4.3)	15 (48.4)
Inconclusive	2 (1.3)	2 (6.4)

Bronchoscopy was performed within 24 hours of admission in 79% of those with bronchial foreign bodies, and laryngotracheoscopy in 51% of the cases with foreign bodies in the larynx or trachea. Of the foreign bodies removed, 98% were done by laryngoscopy, tracheoscopy, and/or bronchoscopy. In 15%, a second or a third bronchoscopy was needed, either because the foreign body was not found in a previous procedure (9%) or because an incomplete removal was made (6%). Two children coughed out the foreign body and one patient needed a thoracotomy.

One patient died during the bronchoscopic procedure owing to cardiac arrest. Tracheostomy was performed in five patients because of laryngeal edema. Mediastinal and subcutaneous emphysema were seen in three patients, pneumothorax in two patients, and convulsion in one patient.

An improvement in the fluoroscopic appearance of the chest within six days after endoscopy was seen in 75% of all children in whom abnormalities were seen before the endoscopic procedure (Table 8).

Table 6.—Lodgment Site of Inhaled Foreign Bodies

Site (N = 200)	No. (%)
Right main bronchus	83 (41.5)
Left main bronchus	69 (34.5)
Trachea	27 (13.5)
Larynx	8 (4)
Lobar	9 (4.5)
Multiple	2 (1)
Unknown (coughed out)	2 (1)

Table 7.—Nature of Inhaled Foreign Bodies

Foreign Body (N = 200)	No. (%)
Peanuts	93 (46.5)
Sunflower seeds	46 (23)
Improper food materials (bones, fruit skins, pips, eggshells)	25 (12.5)
Proper food materials (excluding peanuts, sunflower seeds)	22 (11)
Plastics or metallic bodies	8 (4)
Unidentified	5 (2.5)
Tooth	1 (0.5)

Table 8.—Time Lapse From Foreign Bodies' Removal to Signs of Improvement on Chest Fluoroscopy

	Cases (N = 155)
No. of Days	No. (%)
1-3	86 (55.5)
4-6	31 (20)
7-10	23 (14.8)
11-20	11 (7.1)
> 20	4 (2.6)

COMMENT

In accordance with the findings of Aytac et al,[3] the greatest danger period of foreign body aspiration is below the age of three years. Maximal

frequency was noted between 1 to 2 years of age, this observation being reported also by others.[4-6] At this age, anything is likely to go into the child's mouth, and without the molar teeth he cannot chew certain edibles finely enough to swallow them.[7] Others[3,7,8] have reported a male-female ratio of 2:1. Pyman[8] hypothesized that this ratio can be explained by the more adventurous and inquisitive nature of males.

The fact that 18% of all children arrived at the hospital more than a month after aspiration is disquieting, bearing in mind that a positive history of aspiration was obtained in 73% of those children. This finding necessitates more watchfulness and accurate history-taking in every child suffering from respiratory symptoms and/or signs.

Manifestations of Aspiration of a Foreign Body

Almost every respiratory symptom or sign might be due to the aspiration of a foreign body. Those manifestations are determined by a number of factors, the most important of which follow.

The Effect of the Foreign Body on the Airflow.—This effect may be in the form of a check, stop, ball, or bypass valve.[9] Accordingly, the effect of the foreign body on the airflow may be altered with every change in its site of lodgment, and this depends on the foreign body's size and shape.[8-10]

Nature of the Foreign Body.—A foreign body of vegetable origin causes the greatest difficulties especially if retained for a considerable time.[9-11] Because of the small group of inorganic foreign bodies in our study, any difference between the patients who aspirated organic and those who aspirated inorganic foreign bodies cannot be statistically significant. All foreign bodies inhaled by infants less than 1 year of age were food materials. This surprising fact may be due to the alertness of the parents to choose adequate infant toys on the one hand and the neglect of proper food preparation (peeling, grinding, mashing, etc) on the other hand. Hence, we are obliged to bring to the parents' notice the importance of proper preparation of infant food.

Latent Period After Foreign Body's Aspiration.—Surface sensory receptors of the respiratory tract become adapted to prolonged pressure caused by a foreign body once lodged in its site. Coughing will not recur until other sensory receptors are stimulated either by movement of the foreign body or by secretions. Consequently, the latent period may vary from hours to months or years.[8]

Although it is impossible to separate the clinical manifestations of the foreign body according to all the aforesaid factors, and such a classification will be useless to the physician, the differences between the clinical manifestations of the bronchial and the laryngotracheal foreign bodies justify such a division. The most common clinical manifestations of the laryngotracheal foreign bodies seen in more than 62% of our patients were dyspnea, cough, and stridor. Those manifestations of the bronchial foreign bodies seen in more than 58% of our patients were cough, decreased air entry, dyspnea, and wheezing (Table 3).

Despite the radiolucency of the majority of the foreign bodies,[3,6,7] their existence is often suggested owing to the secondary effects they produce on the lungs. The radiological investigation must consist of anteroposterior and lateral films in both phases of respiration.[3,7-9,12] Our results demonstrate the limitations of plain chest roentgenograms in the diagnosis of aspirated foreign bodies (1) since 60% of the children with foreign bodies in their larynges or tracheas had normal chest roentgenograms; (2) since 16% of the children with bronchial foreign bodies had normal chest roentgenograms; and (3) since findings of pneumonia per se in chest roentgenograms may impede making the correct diagnoses. Infiltration can be due to primary pneumonia or infected atelectasis after aspiration of a foreign body. This fact is well known and some authors[13] have suggested the use of fluoroscopy as an additional diagnostic procedure. Abnormal behavior of mediastinal shadow during the respiration is sought by means of fluoroscopy.

Types of Mediastinal Changes

Six types of mediastinal changes in shape and size during inspiration have been described by Lederer et al.[14] The two most important are included here.

Inspiratory Widening of Mediastinal Shadow.—This widening is a diagnostic sign of laryngeal, tracheal, or both main bronchi obstruction. Inspiration becomes forced, and intrathoracic pressure becomes much lower than the atmospheric pressure. This pressure gradient causes increased venous return into the heart, and the heart's shadow demonstrates inspiratory widening on fluoroscopy. This widening can also be caused physiologically during a forced inspiration voluntarily closing the glottis, and therefore, the widening of the heart's shadow may be seen if a cry or a forced shout precedes inspiration.

Inspiratory Shift of Mediastinal Shadow.—This shift indicates a unilateral bronchial obstruction. In lesser degrees of impairment to air inflow, this sign is visible only at the beginning of inspiration ("initial shift").

Diagnostic and Therapeutic Considerations

A comparison of the data of Tables 4 and 5 shows that fluoroscopy increases significantly the percentage of accurate diagnoses in cases of bronchial foreign bodies (90% vs 62%). Whereas the discrepancy between the fluoroscopic and bronchoscopic findings was 8.6% in the bronchial foreign bodies, that between the fluoroscopic and bronchoscopic findings in the laryngotracheal foreign bodies amounted to 61% of the cases (normal in 48% and mediastinal shift in 13%). Since inspiratory widening of the mediastinal shadow can be the result of upper airway obstruction, it can be concluded that fluoroscopic examination can be sometimes misleading in the diagnosis of laryngotracheal foreign bodies. These misleading fluoroscopic results impeded early intervention (within 24 hours of admission) in 15 children with laryngotracheal foreign bodies.

Whereas the diagnostic problems of bronchial foreign bodies can be solved by using the lung scanning tech-

nique,[15,16] the diagnostic difficulties of the laryngotracheal foreign bodies, which are not rare in childhood as some have suggested,[17] are not solved yet. Some special roentgenographic techniques failed in detecting foreign bodies in this area. Doust et al,[18] who studied the xeroradiographic detection of laryngotracheal foreign bodies in killed dogs, found that the detection of foreign bodies depends on their size and nature. Moreover, the high radiation dosage necessary in xeroradiography further limits its use in children. Rosenfield et al[19] found that xeroradiography contributed to the diagnosis of upper airway obstruction in only one out of nine cases. Tomography of the airway is impossible in infants and small children who cannot suspend respiration for the time of exposure.[19] Meanwhile, one must attach great importance to the history and clinical manifestations in those cases with normal findings from radiologic examination.

Endoscopy was performed, when possible, as an elective procedure, in the forenoon when the team was at its best and hospital ancillary services were available. The endoscopic procedure needs teamwork and necessitates good communication between the endoscopist and anesthesiologist. Careful preparation of the instruments and specific instructions to the endoscopic team will reduce morbidity and mortality. Management of endoscopy took into account Holinger's advice:[20] "If two hours are spent in such preparation, the safe endoscopic removal of the foreign body may take only two minutes. But if only two minutes are taken for preparation, the endoscopist may find himself attempting makeshift ineffective procedures for the next frustrating two hours."

Every patient arrived at the operating room with an intravenous infusion in place that provided fluids and a convenient route for administering drugs. Atropine sulfate was used for premedication to block the parasympathetic activities caused by the use of the bronchoscope and to reduce the patient's reflexes.

The anesthetic treatment commenced with the introduction of halothane, nitrous oxide, and oxygen. The patient then received intravenously an adequate dose of succinylcholine chloride, and after relaxation, the bronchoscope was inserted, through which the anesthetic gases continued to be administered. When the foreign body was removed, the patient received hydrocortisone acetate intravenously to avoid edema of the larynx, administration of anesthetic gases was stopped, and 100% oxygen was provided until normal respiration was restored.

Patients with bronchial foreign bodies of prolonged sojourn accompanied by infection received a brief but intensive course of antibiotics. In some cases, 8 mg/kg/day of hydrocortisone acetate were added to the therapeutic regimen to reduce endobronchial edema around the foreign body and to ease subsequent extraction. The antibiotic course was continued after endoscopy. Patients with foreign bodies of short sojourn and uncomplicated removal did not have postoperative therapy. Our low rate of complications (6%) after bronchoscopy is in accordance with that of Daniilidis et al[5] (5%), and much lower than those of Teig and Grønas[4] (12%), and Harboyan and Nassif[6] (30%).

The fact that in 15% of all patients a second or even a third bronchoscopy was performed indicates that a normal bronchoscopic result does not exclude the presence of a foreign body in the airway and that the finding of one foreign body does not exclude the presence of another. Therefore, an additional bronchoscopy must be performed if the clinical symptoms continue after normal or abnormal findings of a bronchoscopic procedure. Occasionally, clinical signs will improve after incomplete removal of one or more foreign bodies. Since 75% of the children had fluoroscopic improvement within six days after endoscopy (Table 8), a follow-up chest fluoroscopy should be routinely performed after one week, even if there are no clinical signs.

Finally, the physician should bear in mind that a foreign body in the respiratory tract can result in a variety of respiratory symptoms and signs and that awareness and alertness to the existence of a foreign body in the airway can save much trouble, morbidity, and mortality in infants and children.

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References

1. Weston JT: Airway foreign body fatalities in children. *Ann Otol Rhinol Laryngol* 74:1144-1148, 1965.
2. Steichen FM, Fellini A, Einhorn AH: Acute foreign body laryngotracheal obstruction: A cause for sudden and unexpected death in children. *Pediatrics* 48:281-285, 1971.
3. Aytac A, Yurdakull Y, Coskum I, et al: Inhalation of foreign bodies in children: Report of 500 cases. *J Thorac Cardiovasc Surg* 74:145-150, 1977.
4. Teig E, Grønas HE: Foreign bodies in the lower respiratory tract. *Acta Otolaryngol*, suppl 224, 1966, pp 429-430.
5. Daniilidis J, Symeonidis B, Triaridis K, et al: Foreign body in the airway: A review of 90 cases. *Arch Otolaryngol* 103:570-573, 1977.
6. Harboyan G, Nassif R: Tracheobronchial foreign bodies: A review of 14 years' experience. *J Laryngol Otol* 84:403-412, 1970.
7. Kim IG, Brummitt WM, Humphry A, et al: Foreign body in the airway: A review of 202 cases. *Laryngoscope* 83:347-354, 1973.
8. Pyman C: Inhaled foreign bodies in childhood: A review of 230 cases. *Med J Aust* 1:62-68, 1971.
9. Chatterji S, Chatterji P: The management of foreign bodies in the air passages. *Anaesthesia* 27:390-395, 1972.
10. Tucker GF, Turtz MG: Foreign bodies in the air and food passages, in Ferguson CF, Kendig EL (eds): *Pediatric Otolaryngology*. Philadelphia, WB Saunders Co, 1972, vol 2, pp 1242-1270.
11. Davis CM: Inhaled foreign bodies in children: An analysis of 40 cases. *Arch Dis Child* 41:402-406, 1966.
12. Benjamin B, Vandeleur T: Inhaled foreign bodies in children. *Med J Aust* 1:355-358, 1974.
13. Adler D, Fuller D: Foreign bodies in the trachea and bronchi: Review of 100 cases in children. *S Afr Med J* 27:1155-1161, 1953.
14. Lederer KT, Munk J, Kleinhaus U: Inspiratory changes of the mediastinal shadow in respiratory obstruction in children. *Harefuah* 70:115-118, 1966.
15. Vered J, Rosen G: Foreign bodies in airways in children. *Harefuah* 91:280-282, 1976.
16. Rudavsky AZ, Leonidas JC, Abramson AL: Lung scanning for the detection of endobronchial foreign bodies in infants and children. *Radiology* 108:629-633, 1973.
17. Dunbar JS: Upper respiratory tract obstruction in infants and children. *Am J Roentgenol* 109:227-246, 1970.
18. Doust BD, Ting YM, Chuang VP: Detection of aspirated foreign bodies with xeroradiography. *Radiology* 111:725-727, 1974.
19. Rosenfield NS, Peck DR, Lowman RM: Xeroradiography in the evaluation of acquired airway abnormalities in children. *Am J Dis Child* 132:1177-1180, 1978.
20. Holinger PH: Foreign bodies in the air and food passages. *Trans Am Acad Ophthalmol Otolaryngol* 66:193-210, 1962.

Incidence of Meconium Abnormalities in Newborn Infants With Cystic Fibrosis

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• Review of the newborn nursery notes of 87 infants who had cystic fibrosis without meconium ileus (MI) indicated that 12 of them had clinical features consistent with the meconium plug syndrome (MPS). This high incidence of meconium abnormalities suggests that MI and the MPS probably represent different gradations of the same underlying pathologic abnormality. The findings further suggest that a quantitative pilocarpine iontophoresis sweat test be performed in every newborn infant with any type of meconium abnormality, including the spontaneous passage of meconium plugs.

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Meconium ileus (MI), in which there is obstruction of the small bowel by sticky meconium, has been reported to occur in approximately 7% of newborn infants with cystic fibrosis (CF).[1] The meconium plug syndrome (MPS), in which there is transient distal colonic obstruction associated with the passage of meconium plugs, has also been reported in CF.[2,3] It has been suggested[3] that MI and MPS may represent different manifestations of the same underlying pathologic abnormality: both are related to the presence of abnormal meconium and differ only in the site and severity of obstruction. If this hypothesis is correct, the frequent occurrence of MI in infants with CF and the apparent rarity of MPS is curious. The purpose of the present study, therefore, was to examine the nursery records of patients with documented CF to determine the incidence of all types of meconium abnormalities in the newborn period in this group of patients.

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SUBJECTS AND METHODS

From July 1, 1973, through November 30, 1978, 149 patients with CF were seen at the Johns Hopkins Hospital, Baltimore. The diagnosis of CF was based on characteristic clinical features and a positive quantitative pilocarpine iontophoresis sweat test (Cl^- concentration >60 mEq/L). Of the 149 patients, 13 (8.7%) had MI. An attempt was made to obtain the newborn nursery records of the remaining 136 patients. Because of problems with record retrieval, however, including lost records and incomplete nursery notes, we were able to use the records of only 87 of the 136 patients. Of these 87 patients, 12 had features consistent with the MPS in the newborn period (Table). Of the 12 infants, seven had abdominal distention, five had vomiting, and five had palpable abdominal masses. Six were treated by the insertion of rectal tubes, suppositories, or enemas. Three infants (patients 3, 4, and 12) passed meconium plugs or abnormal meconium but had no associated problems or abnormal findings. At the time the diagnosis of CF was established, the parents of only five of the 12 patients gave a history of any intestinal problem in the nursery.

RESULTS

Meconium ileus occurred in one of 12 black patients and in 12 of 137 white patients. Among patients without MI, a picture consistent with the MPS occurred in three of five black patients and in nine of 82 white patients. All 75 infants without evidence of meconium obstruction passed their first meconium stool within 36 hours. A review of the newborn nursery notes of 100 infants discharged from two full-term nurseries in Baltimore indicated that all infants passed a meconium stool by 36 hours of age, and in no instances were meconium plugs or abnormal meconium described.

COMMENT

The MPS may occur in association with prematurity,[4] hypotonia,[5] hypermagnesemia,[6] respiratory distress syndrome,[7] sepsis,[7] and hypothyroidism,[4] and as the earliest manifestation of Hirschsprung's disease[4,8] and CF.[2,3] Our findings confirm that the MPS may be the earliest manifestation of CF. It has also been stated[9,10] that newborn infants with CF may pass plugs of abnormal meconium, either in a spontaneous fashion or in response to enemas or digital rectal examination. However, the incidence of these plugs and details of such cases have not been reported. In the present series, the occurrence of meconium abnormalities consistent with the MPS in 12 of 87 newborns with CF but without MI is striking. There was a wide range of manifestations, including three infants who passed abnormal meconium without associated problems, six infants who had abdom-

Patients With Findings Consistent With the Meconium Plug Syndrome

Patient/ Race	Description of Meconium	Distention*	Vomiting*	Treatment	Age at Diagnosis of CF
1/B	Large meconium plugs	+	+	Enemas	1 mo
2/W	Meconium plugs, hard gummy meconium	+	+	. . .	4½ mo
3/W	2 Meconium plugs passed first day	—	—	. . .	2½ yr
4/W	1 Meconium plug passed day 2	—	—	. . .	5 mo
5/W	Large meconium plugs, palpable sausage-shaped abdominal masses	+	—	Rectal tube, enemas	1 wk
6/W	Large meconium plugs, palpable fecal masses	—	+	Rectal suppositories	3 mo
7/W	Large meconium plug, palpable abdominal masses	+	+	Nasogastric tube, enema, rectal suppositories	3 mo
8/B	Meconium plug, palpable abdominal masses	+	—	. . .	6 mo
9/W	Palpable sausage-shaped abdominal masses	+	—	. . .	2½ yr
10/B	Delayed passage of meconium, no description of meconium	+	—	Nasogastric and rectal tubes	3 yr
11/W	Large mucus plug with meconium stool	—	+	Enema	4 mo
12/W	3 Dark-green "glue-like" stools	—	—	. . .	18 mo

* + indicates present; —, absent.

inal distention *or* vomiting, and three infants who had abdominal distention *and* vomiting. Although a contrast enema was performed in only one of these infants (patient 1), the transient nature of the obstruction and the uncomplicated course are more consistent with the MPS than with MI. This spectrum of abnormalities, from the spontaneous passage of plugs of abnormal meconium to the full-blown picture of MI supports the hypothesis that the MPS and MI may represent gradations of the same underlying pathologic abnormality, differing only in degree of severity and site of obstruction.

The etiology of the meconium abnormalities seen in these patients remains unclear. The MPS[11] and MI[12] have been associated with pancreatic exocrine deficiency in the absence of CF, and MI has been described in infants with CF in whom there was widespread mucous gland hyperplasia of the intestinal tract but no histologic evidence of pancreatic involvement.[13] It is possible, therefore, that the meconium abnormalities seen in our patients were due to a combination of abnormal mucoprotein secretions by the intestinal glands and pancreatic exocrine deficiency.

It is of interest that the parents of only five of the 12 infants with meconium abnormalities other than MI were aware that there had been an intestinal problem during the newborn period. This may account for the "apparently" low incidence of MPS in infants with CF. In three of the cases in which the parents were unaware of a problem, the infants passed abnormal meconium but had no associated symptoms and required no therapy. In four cases, however, the infants had distention and/or vomiting. Although the number of cases is small, the occurrence of meconium abnormalities in at least four of 12 black patients is pertinent in view of the high incidence of meconium ileus equivalent reported in black patients with CF.[14]

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References

1. *Survival Studies of Patients With Cystic Fibrosis.* Atlanta, Cystic Fibrosis Foundation, 1977.

2. Grossman H, Berdon WE, Baker DH: Gastro-intestinal findings in cystic fibrosis. *Am J Roentgenol Radiat Ther Nucl Med* 97:227-238, 1966.

3. Rosenstein BJ: Cystic fibrosis presenting with the meconium plug syndrome. *Am J Dis Child* 132:167-169, 1978.

4. Mikity VG, Hodgman JE, Paciulli J: Meconium blockage syndrome. *Radiology* 88:740-744, 1967.

5. Swischuk LE: Meconium plug syndrome: A cause of neonatal intestinal obstruction. *Am J Roentgenol Radiat Ther Nucl Med* 103:339-346, 1968.

6. Sokal MM, Koenigsberger MR, Rose JS, et al: Neonatal hypermagnesemia and the meconium plug syndrome. *N Engl J Med* 286:823-825, 1972.

7. Taybi H, Patterson J: Plain film diagnosis of meconium plug syndrome: Presacral "mass." *Radiology* 104:113-114, 1972.

8. Gillis DA, Grantmyre EB: The meconium plug syndrome and Hirschsprung's disease. *Can Med Assoc J* 92:225-227, 1965.

9. Di Sant'Agnese PA, Lepore MJ: Involvement of abdominal organs in cystic fibrosis of the pancreas. *Gastroenterology* 40:64-74, 1961.

10. Kopel FB: Gastrointestinal manifestations of cystic fibrosis. *Gastroenterology* 62:483-491, 1972.

11. Townes PL, Kopelman AE: Meconium plug syndrome, cystic fibrosis, and exocrine pancreatic deficiency. *Am J Dis Child* 132:1043-1044, 1978.

12. Auburn RP, Feldman SA, Gadacz TR, et al: Meconium ileus secondary to partial aplasia of the pancreas: Report of a case. *Surgery* 65:689-693, 1969.

13. Oppenheimer EH, Esterly JR: Cystic fibrosis of the pancreas: Morphologic findings in infants with and without diagnostic pancreatic lesions. *Arch Pathol* 96:149-154, 1973.

14. Stern RC, Doershuk CF, Boat TF, et al: Course of cystic fibrosis in black patients. *J Pediatr* 89:412-417, 1976.

Review

Trace Elements in the Fetus and Young Infant

II. Copper, Manganese, Selenium, and Chromium

Jonathan C. L. Shaw, FRCP

The trace elements are so called because they constitute less than 0.01% of the weight of the human body; however, despite their relative scarcity, their atoms are present in large numbers and each is believed to play an important role in human growth and development. For example, chromium is perhaps one of the least abundant trace elements in the body and yet even a single hepatocyte contains about 4.5 million atoms of this element. The name "trace element" is, of course, quite arbitrary and survives from the time when early investigators were experiencing great difficulties in measuring these substances; the introduction of more sophisticated techniques has resulted in an enormous increase in our understanding of the role these elements play in metabolism.

This review deals with zinc, copper, manganese, selenium, and chromium. The amount of space devoted to each element is not intended to correspond to its importance in metabolism, but rather to reflect the extent of our current knowledge. This review is being published in two parts; part I, published in the previous issue, dealt with zinc, while part II, which follows, deals with copper, manganese, selenium, and chromium.

COPPER

Though it has been known for more than 100 years that copper is a component of hemocyanin, the respiratory pigment of snails,[1] its possible significance in human metabolism was not appreciated until 1928, when Hart et al[2] showed copper to be an essential nutrient for the rat. Copper is now known to be a component of a number of copper metalloenzymes.[3,4] These enzymes generally bind between 1 and 8 gram-atoms of copper per mole, and the presence of copper is essential for their enzymic activity. The function of the copper seems to be related to its ability to engage in oxidation reduction reactions ($Cu^{2+} \rightleftharpoons Cu^{+}$).

Copper Enzymes

A list of some copper enzymes is given in Table 1. Ceruloplasmin is a blue glycoprotein (molecular weight, 160,000) and contains 8 gram-atoms of copper per mole (0.32%). It is synthesized in the liver and is released into the circulation, where it accounts for the majority of the plasma copper. In the newborn pig, ceruloplasmin exists in two forms that differ in their enzymatic activity and copper content. The neonatal type, predominant at birth, remains constant, whereas the adult type increases postnatally.[5] Osaki et al[6] have advanced the hypothesis that ceruloplasmin is an important ferroxidase that facilitates the release of iron from iron stores by oxidizing ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) prior to its incorporation into plasma transferrin.

Cytochrome C oxidase is the terminal enzyme of the cytochrome chain and contains 1 gram-atom of copper per mole of haem A. It is located in the mitochondria and, as an electron donor, catalyzes the reduction of molecular oxygen to water. This enzyme therefore occupies a vital position in energy metabolism. Its concentration falls in the brain and liver of the copper-deficient animal and may account *inter alia* for the hypothermia of copper deficiency.

Lysyl oxidase catalyzes the cross linking of the polypeptide chains of collagen and of elastin. The enzyme has a molecular weight of 60,000 daltons and contains 0.14% copper by weight.[3] Tyrosinase catalyzes the first two steps in the synthesis of melanin, and genetically determined absence of this enzyme results in albinism.

Copper Deficiency in Animals

Anemia and neutropenia are regular features in copper-deficient animals. The early work of Hart and colleagues[2] has been reviewed by Lardy.[7] They showed that the anemia of rats fed on a milk diet from weaning could not be corrected by administration of iron alone, but that it was cured by administration of the ash of liver, lettuce, or corn. By precipitating the copper from acid extracts of the ash with hydrogen sulfide, they were able to show that it was the copper in the ash that was essential for the full reversal of the anemia. Apart from its association with iron in cytochrome C oxidase, copper interacts with iron metabolism at two points: the release of iron from iron stores, and the incorporation of iron into haem.

According to the Osaki hypothesis,[6] ceruloplasmin is a ferroxidase that is essential for the mobilization of iron from iron stores. This has been studied in newborn pigs and the work has been recently reviewed by Lee et al.[8] In copper-deficient swine, ceruloplasmin levels fell to less than 1% of normal and there was an associated fall in serum iron levels. Iron absorption was diminished and iron accumu-

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lation was observed in the intestinal mucosal cells and adjacent macrophages, suggesting a difficulty in release of iron from the mucosal cells. Injection of parenteral iron in the form of colloidal iron oxide or damaged erythrocytes resulted in trapping of the iron in the iron stores and reticuloendothelial cells of these copper-deficient animals. Injection of ceruloplasmin then resulted in a prompt release of iron from the iron stores, as judged by a rise in plasma iron concentration. These data are consistent with the role of ceruloplasmin as a ferroxidase. However, the extreme variability of ceruloplasmin oxidase activity among species[9] and its virtual absence in the plasma of the turkey and the peacock[10] and certain crocodiles[11] shows that much remains to be discovered.

There is now much evidence to link copper with the synthesis of haem that takes place within the mitochondria and involves the enzyme ferrochelatase and the precursors protoporphyrin IX and Fe^{2+}. Since both iron and protoporphyrin accumulate within the erythroid cells of copper-deficient animals, the precursors of hemoglobin are not lacking in the marrow, and failure to release iron from the iron stores cannot, therefore, account entirely for the anemia of copper deficiency. Copper deficiency is thought to interfere with haem synthesis in three ways: by diminishing iron transport into the mitochondria,[12] by inhibiting the activity of ferrochelatase,[13] and possibly by reducing the concentration of the copper-iron enzyme cytochrome C oxidase. Lee et al[8] reviewed their evidence that an intact cytochrome chain is necessary for the synthesis of haem; uncoupling oxidative phosphorylation with 2,4-dinitrophenol did not inhibit haem synthesis, indicating that electron transport rather than adenosine triphosphate synthesis was the essential function. They postulated that the cytochrome chain, by providing a source of electrons, was necessary to reduce ferric (Fe^{3+}) iron to its ferrous form (Fe^{2+}) prior to incorporation into protoporphyrin IX. It seems, therefore, that events in the mitochondria may be more important determinants of the anemia of copper deficiency than diminished ferroxidase activity in the plasma. Neutropenia was observed by Wintrobe et al[14] in copper-deficient swine and has been reported in many species since, including man; however, its cause is unknown.

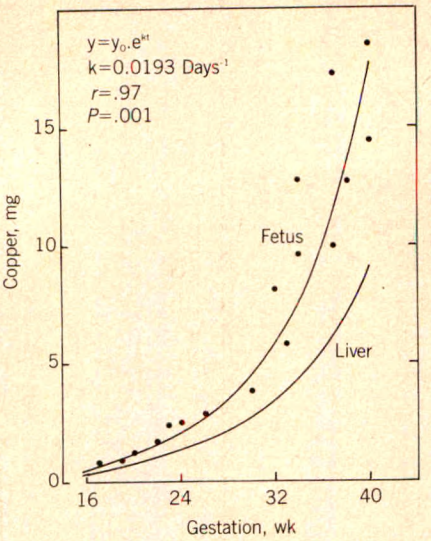

Fig 1.—Changes in the copper content of the human fetus and fetal liver with gestation.[18,19]

Collagen and Elastin Synthesis

In copper-deficient animals, aneurysms of major vessels readily develop, and they may cause death from hemopericardium or from hemothorax as a result of aortic rupture.[1] The collagen and elastin of these animals has been found to be abnormal, with reduced cross linking and consequent reduction in strength and elasticity. These effects result from the reduced activity of lysyl oxidase.[3] The bones become brittle and fracture easily, and roentgenograms show blurring and cupping of the metaphysis reminiscent of scurvy. The disorder of collagen metabolism is partly responsible, but reduced activity of ascorbic acid oxidase (another copper enzyme) may also play a part. Hair abnormalities described as "steely hair" are found in copper-deficient animals and are attributed to defective cross linking of the keratin molecule. Depigmentation of hair, so striking in copper-deficient black sheep, results from impairment of tyrosinase activity.

Effects of Copper Deficiency During Gestation

Copper deficiency during pregnancy in sheep results in the ataxic disease "swayback" or "enzootic neonatal ataxia" in the newborn lamb. In affected sheep, there is extensive demyelination of the CNS, and the brain mitochondria show depletion of cytochrome C oxidase.[1] These changes are observed in a number of other species.[15] Anormalities in elastin occur and extensive changes in the myocardium of copper-deficient rat pups have been reported with depletion of myocardial cytochrome oxidase.[16,17]

Copper in the Human Fetus and Newborn

Copper must enter the embryo from the earliest moments of gestation, but little seems to be known about its role in this early period. Figure 1 shows the accumulation of copper by the human fetus.[18] At term, about half the copper in the body is present in the liver,[19] where it is bound to a protein recently identified as a metallothionein.[20,21] After birth, the concentration of copper in the liver falls as the copper is used for growth, though the total amount ultimately increases because of the increase in size of the organ.[18] Estimates of the daily rate of accumulation of copper by the human fetus are given in Table 2. The value of 0.051 mg/kg/day for a fetus growing along the 50th percentile is lower than previous estimates,[22] which were based on the exponential regression analysis given in Fig 2, and did not take into account the unusually high body weight of the mature fetuses in Widdowson's series.[18] These revised rates of accumulation correspond quite closely to those recommended for intravenous feeding of preterm infants.[23]

Copper in Blood

In adults, about 49% of the copper in whole blood is in the RBCs, where the concentration is about 110 μg/dL of RBCs.[14] Unlike the plasma copper, there is very little species variation in the RBC copper[10]; about 60% is present in the enzyme superoxide dismutase. The concentration of this enzyme is high in RBCs of the fetus and falls

Table 1.—Some Copper Enzymes

Enzyme	Source
Cytochrome C oxidase	Mitochondria
Superoxide dismutase	Erythrocytes
Ceruloplasmin	Plasma
Tyrosinase	Skin
Dopamine β hydroxylase	Adrenal gland
Lysyl oxidase	Cartilage, aorta
Diamine oxidase	Kidney

Table 2.—Calculated Estimates of the Daily Rate of Accumulation of Copper by a Human Fetus In Utero*

Gestation, wk	Percentile, mg/Day		
	10	50	90
24	0.029	0.046	0.069
26	0.037	0.052	0.074
28	0.047	0.063	0.085
30	0.058	0.076	0.101
32	0.071	0.094	0.125
34	0.088	0.120	0.161
36	0.112	0.148	. . .

*This is a revision of previous estimates.[22] For these calculations, the amount of copper in the fetal bodies was calculated from the concentrations reported by Widdowson and Dickerson[18] and the body weights reported by Lubchenko et al.[103] The rates were calculated by exponential analysis. The specific accumulation rates for infants growing along the different percentiles are as follows: tenth percentile, 0.055 mg/kg/day; 50th percentile, 0.051 mg/kg/day; 90th percentile, 0.043 mg/kg/day (previous estimates were 0.078 to 0.092 mg/kg/day[22]).

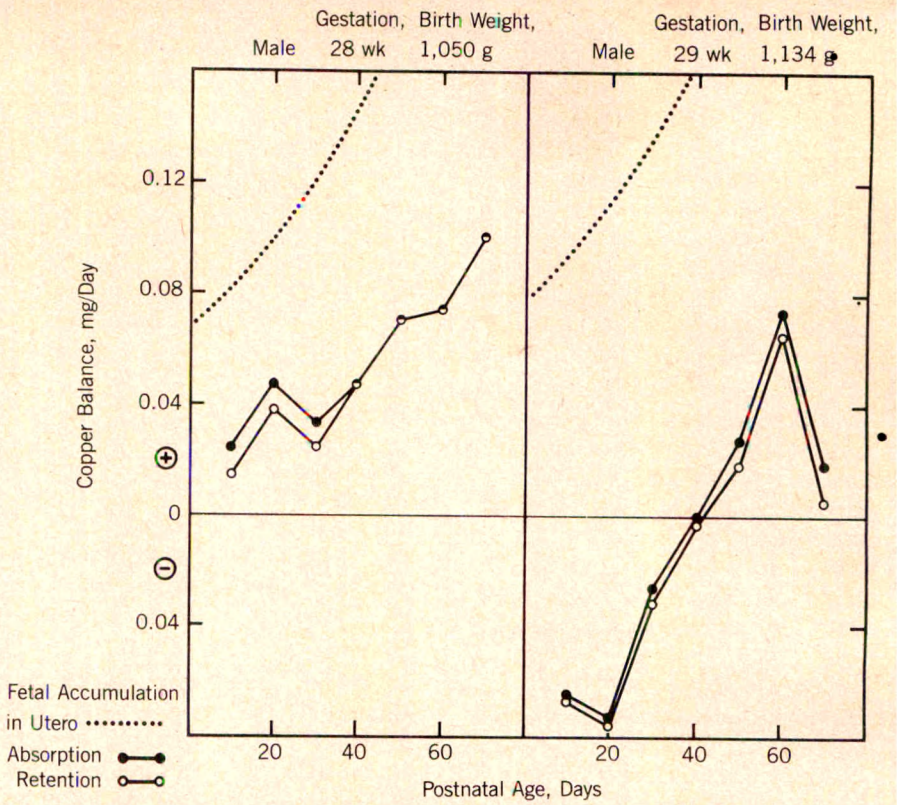

Fig 2.—Contrasting examples of copper balance in two preterm infants.[52] Balances commenced on tenth day of life and lasted three days. They were repeated every ten days until infant was discharged home. Estimated fetal accumulation rate is given for comparison.[103]

toward term.[24] The remaining 40% of the RBC copper is in a labile pool in equilibrium with plasma copper.[4] In plasma, about 96% of the copper is present as ceruloplasmin[25] and only about 8% of the ceruloplasmin is present as apoceruloplasmin.[26] In newborn infants, Henkin et al[27] showed that 86% of the plasma copper was retained by a filter that excluded particles "substantially in excess of 50,000 daltons." Hence, ceruloplasmin-bound copper in newborns may be a smaller percentage of the total than it is in adults. To my knowledge, no attempt to characterize human fetal or neonatal ceruloplasmin has yet been reported.

The majority of the copper not bound to ceruloplasmin is bound to serum albumin. The amino acid sequence of the albumin binding site has recently been determined and a structure for it proposed, and though there are species differences, the capacity to bind copper seems dependent on the histidine residue at the binding site.[28,29] The albumin-bound copper is relatively labile and is in equilibrium with copper bound to amino acids and to oligopeptides. Blood concentrations of copper and ceruloplasmin are given in Table 3. Plasma copper levels are higher in women than in men and both the total copper and ceruloplasmin levels virtually double in women taking oral contraceptives. During pregnancy, copper and ceruloplasmin levels rise. The highest levels are seen at term and fall to normal by about 6 weeks after delivery. Paradoxically and in contrast to zinc, the total copper and ceruloplasmin levels are low at birth in full-term infants and may rise to above adult levels between 1 and 6 years of age (Table 4).

Copper in Milk

The copper content of human milk is given in Table 5. According to the data of Nassi et al,[30] the concentration of copper, unlike that of zinc, seems to be no higher in colostrum than in mature milk. However, Hambidge[31] has recorded a mean value of 119 μg/dL on days four to seven after birth, and Cavell and Widdowson[32] observed a mean value (± standard deviation) of 68 ± 8 μg/dL on days five to eight after birth. The copper concentration seems to fall toward the end of lactation. At an intake of 150 mL/kg/day of mature milk, an infant would receive about 60 μg/kg/day. Cavell and Widdowson[32] showed that full-term infants receiving breast milk were in negative balance, averaging −0.009 mg/kg/day (range, +0.029 to −0.066 mg/kg/day). Kleinbaum[33] reported similar results. How long these negative balances persist is not known.

Copper Absorption and Excretion

Copper is thought to be absorbed complexed with amino acids by an active process. Some of the copper in the mucosal cell is associated with

metallothionein. The copper is transported in the blood to the liver, where ceruloplasmin synthesis takes place. The principal route of excretion of copper from the body is in the bile, where copper is found complexed to proteins and low-molecular-weight ligands. The protein-bound copper in bile is apparently poorly reabsorbed, though the remainder enters into an enterohepatic circulation.[4]

Copper Deficiency in Infants

Following up the experimental work of Hart et al,[2] Elvehjem[7,34] showed that copper might be effective in treating anemic infants. However, these studies included neither measurements of plasma copper nor an untreated control group, and though copper appeared to be effective, this fact was not really established. This work was followed by a number of reports of hypocupremia in anemic infants, some of whom responded to therapy with copper.[35-37] Recently, Graham and Cordano[38] have reviewed their work on copper deficiency in malnourished infants rehabilitated on a cow's milk diet low in copper. They found a fall in copper and ceruloplasmin levels to be the earliest change, the latter falling to almost undetectable levels. Neutropenia and anemia followed, the latter being typically resistant to therapy with iron. Later, bone changes reminiscent of scurvy developed, with occasional fractures. Since this work was published, there have been several reports of hypocupremia and copper deficiency developing in patients receiving copper-free total parenteral nutrition.[39-46] The principal features of the syndrome are now well described and are summarized in Table 6.

The Preterm Infant

To my knowledge, there are now three case reports in the literature of well-documented copper deficiency in small preterm infants fed a milk diet low in copper[47-49] and others where it was suspected but not established.[50,51] In the proven cases, the infants all weighed less than 1,200 at birth and their deficiency state developed between three and six months postnatally.[47-49] In addition, four of the 14 cases of hypocupremia reported by Schubert and Lahey[36] were premature infants. The reasons for the particular vulnerability of the preterm infant have been discussed earlier. Breast milk given at 200 mL/kg/day provides copper just in excess of the estimated fetal accumulation rate (Table 5), but not all of it is absorbed. Dauncey et al[52] have shown that the preterm infants they studied given breast milk were, on average, in negative balance until the 35th day of life, and even those infants in positive balance never equalled intrauterine accumulation rates (Fig 2). This confirms the earlier observations of Kleinbaum,[33] who found negative copper balances in all the low birth weight infants he studied.

The changes in plasma copper levels in preterm infants measured in my laboratory are given in Fig 3. Unlike the full-term infants, the plasma copper level was high at birth and tended to fall steadily to quite low values. The changes in serum ceruloplasmin levels closely resembled the changes in total copper levels. These results are preliminary and their exact significance is not yet known. Does this fall in copper level, for instance, reflect a deficiency, or is it part of a normal decline resulting in the usual low values at term?

Menkes' Kinky-Hair Disease

This is an X-linked, recessively inherited disease first described by Menkes et al.[53] It is characterized by many of the features of copper deficiency, but apparently without neutropenia and anemia.[54] There are pili torti, typical bone changes, arterial intimal changes, seizures with developmental regression, hypothermia, and the patients generally die before the age of 2 years. Plasma copper and ceruloplasmin levels are very low[26,54-58] and copper absorption is defective.[54,57] Williams et al,[54] by infusing copper as a copper histidine complex, were able to raise plasma copper and ceruloplasmin levels to normal, but, though the

Table 3.—Copper and Ceruloplasmin Concentrations in Maternal and Fetal Blood and in Amniotic Fluid

	Copper, μg/dL ± SD	Ceruloplasmin, mg/dL ± SD
Plasma		
M	92 ± 12*	31 ± 4†
F	107 ± 23*	31 ± 5†
Women receiving oral contraceptives	221 ± 62*	57 ± 21†
Pregnant, 16 wk	162 ± 27*	71 ± 24†
Pregnant, 36 wk	192 ± 24*	
Serum		
Pregnant, term	221 ± 54‡	91 ± 13‡
Cord blood, term	29 ± 11‡	10 ± 6‡
Amniotic fluid		
Clear	31.2 ± 13.3§	. . .
Meconium-stained	30.6 ± 11.0§	. . .

*From Hambidge and Droegmueller.[104]
†From Mondorf et al.[106]
‡From Henkin et al.[105]
§From Favier et al.[107]

Table 4.—Summary of Changes in Serum Copper With Age

Age	μg/dL ± SD
Cord blood	29 ± 11*
5 days	47 ± 9†
1 mo	63 ± 17†
3 mo	81 ± 17†
5 mo	104 ± 25†
6-12 mo	111 ± 19†
6-12 yr	109 ± 17‡

*From Henkin et al.[105]
†From Ohtake.[102]
‡From Ohtake and Tamura.[108]

Table 5.—Changes in Concentration of Copper in Human Milk During Lactation

Lactation	μg/dL ± SD
1 day*	35 ± 4
5 days*	36 ± 8
15 days*	29 ± 4
2-4 wk†	49 ± 3
2 mo†	61 ± 16
3 mo†	42 ± 22
4-7 mo†	29 ± 23

*From Nassi et al.[30]
†From Hambidge.[31]

Table 6.—Syndrome of Copper Deficiency in Infants

Clinical Features
Psychomotor retardation
Hypotonia
Pallor and hypopigmentation
Prominent scalp veins in palpable periosteal depressions
Hepatosplenomegaly
Roentgenographic changes with osteoporosis, blurring and cupping of metaphysis; subperiosteal new bone formation; fractures
Sideroblastic anemia, resistant to iron therapy
Bone marrow shows vacuolated erythroid and myeloid cells with iron deposition in vacuoles
Neutropenia
Plasma copper level usually < 12 μg/dL
Serum ceruloplasmin 2-10 μg/dL

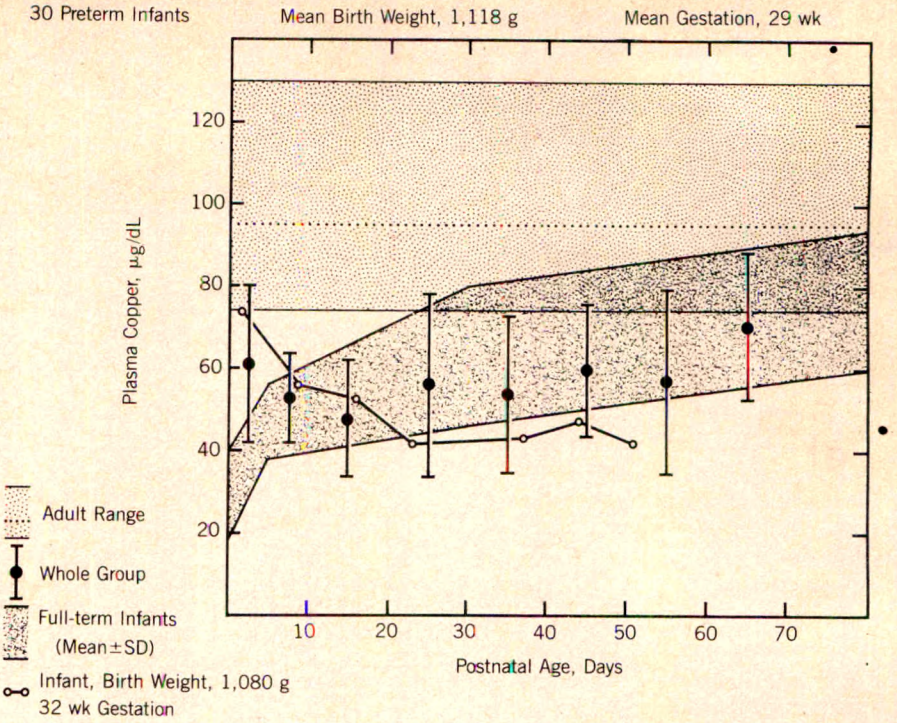

Fig 3.—Changes in plasma copper levels, after birth, in preterm infants compared with values for full-term infants.[102] Adult range in this figure is based on measurements in 20 healthy adult men.

fractures healed, there was no amelioration of the other features of the disease. Since cultured fibroblasts from cases of Menkes' disease handle copper quite differently than do normal cells, it seems likely that the defect is not confined to copper absorption.[59]

Wilson's Disease

Wilson's disease[60] is an autosomal-recessive condition characterized by progressive cirrhosis of the liver, renal malfunction with amino aciduria, glycosuria, neurological degeneration, and Kayser-Fleischer rings in the cornea. These, the major manifestations of the disease, are secondary to the pathological accumulation of copper in the tissues, which results from diminished excretion of copper in the bile.[61,62] The serum ceruloplasmin level is reduced, but is rarely less than 5% of normal.[25] Though the total plasma copper concentration is reduced, because of the low ceruloplasmin level, the labile albumin-bound fraction is increased and accounts for the high urinary copper excretion. A metallothionein with high affinity for copper has been isolated from cases of Wilson's disease,[63] but this finding seems not to have been confirmed. Such a substance is unlikely to account for all the features of the disease. The most effective treatment of Wilson's disease is the use of the chelating agent penicillamine,[64] which, by reducing the total body copper, can arrest the consequences of copper accumulation. However, care is required to avoid zinc deficiency during treatment.[65]

MANGANESE

The metabolism of manganese has been reviewed by Leach.[66] Manganese is a component of comparatively few metalloenzymes; these include pyruvate carboxylase and mitochondrial superoxide dismutase. However, manganese activates a number of enzymes, particularly the glycosyltransferases that are involved in the synthesis of polysaccharides and glycoproteins. The features of manganese deficiency, namely impaired growth, skeletal abnormalities, depressed reproductive function, and ataxia in the newborn,[1] seem to be similar in all species studied. The skeletal abnormalities are thought to be due principally to defective mucopolysaccharide synthesis affecting chondrogenesis. Manganese deficiency in pregnant rats induces profound ataxia in the young.[67] Disturbed ossification of the otic capsule and malfunction of the semicircular canals are responsible for this ataxia. The timing of the deficiency is critical, since provision of manganese to the deficient pregnant rat on day 14 (term, 22 days) completely prevented the defect, whereas manganese supplements given on day 18 had no effect.[67] The ataxia of this deficiency is indistinguishable from a specific genetically determined ataxia due to an otolith defect in pallid mutant mice, which can be prevented by the administration of pharmacological amounts of manganese to the pregnant dams.[68]

The amount of manganese present in the human fetus is not known, though the manganese content of the fetal liver has been analyzed.[19] Human milk contains 1.2 to 2.0 μg of manganese per dL and cow's milk between 3.2 to 5.2 μg/dL.[69] The breast-fed full-term infants studied by Widdowson[70] aged 5 to 8 days were in negative manganese balance. The regulation of manganese in the body is by controlled excretion in the bile,[66] but it is not known whether the negative balances in babies represent an important failure in homeostasis or not. Very little is known about manganese deficiency in man. The only reported case in man exhibited a mild dermatitis, slight reddening of hair, and

depressed vitamin K-dependent clotting factors that did not respond to therapy with vitamin K.[71] Among infants, the preterm infant and those receiving total parenteral nutrition would seem to be the most at risk, and evidence for manganese deficiency should be sought in such cases.

SELENIUM

The importance of selenium as a nutrient was first suspected when it was shown that administration of either selenium or vitamin E could prevent hepatic necrosis of nutritional origin in rats.[72] In 1969, Thompson and Scott[73] separated the effects of selenium deficiency from those of vitamin E deficiency and established selenium as an essential nutrient in vertebrates. To date, the only established function of selenium in man is as a component of the enzyme glutathione peroxidase (GSH-px).[74] This enzyme is distributed widely in the cells of the body and in particular is present in high concentration in the RBCs and the liver. The human enzyme is a tetramer with a molecular weight of 95,000 daltons and contains 4 gram-atoms of selenium per mole.[75] It catalyzes the reduction of hydrogen peroxide using glutathione as a proton donor and functions to protect the cell against peroxide-induced damage. This property, together with its capacity to catalyze the reduction of lipid and other hydroperoxides, is perhaps its principal function in the cell, and accounts for the evident overlap in function with vitamin E, another important antioxidant. Recently, a nonselenium-dependent GSH-px has been described in rat liver.[76] These functions may be of particular significance to phagocytic cells, where peroxides and highly reactive forms of oxygen such as the superoxide radicle[77] are generated during the process of phagocytosis and killing of the ingested organisms. This capacity of the phagocyte to generate the superoxide radicle may be related to the absence of copper-zinc superoxide dismutase from the cytosol.[78]

Virtually nothing seems to be known about selenium in human fetal development. Numerous studies of GSH-px in RBCs have shown lower activities in the newborn and premature infants than in adults.[79-85] Rudolph and Wong[86] have confirmed these observations and have shown that both plasma and RBC selenium and GSH-px levels were lower in the cord blood of full-term infants than in adults. In preterm infants, cord-blood selenium levels were no lower than in full-term infants,[82,83] but in two low-birth-weight infants in whom serial measurements were made, low levels were observed that persisted for several months[82]; however, the functional importance of this trend is not known. The recent report that newborn rats exposed to high concentrations of oxygen adapt with an increase in levels of GSH-px and superoxide dismutase in the lungs suggests that these enzymes play an important part in the capacity of the newborn to resist free-radical damage.[87]

The concentration of selenium in breast milk is reported as being 1.2 to 5.0 μg/dL,[88] but it may be ten times less than this.[89] The concentration in cow's milk is lower than in breast milk and varies with the selenium content of the pastures.[88] Nothing is known about selenium homeostasis in newborn infants, but low levels of plasma selenium have been observed in children on total parenteral nutrition,[90] and low levels of selenium and GSH-px have been found in children on a diet for phenylketonuria or maple syrup urine disease.[91]

CHROMIUM

Chromium has only recently been recognized as being an essential element in man. The subject has been extensively reviewed by Mertz et al.[92-94] Chromium is present in all tissues of the body, but is present in high concentrations in nucleic acids and in certain tissues, such as the caudate nucleus. It forms complexes typically exhibiting a low rate of ligand exchange, which would seem to make it an unsuitable component of the active site of enzymes and more compatible with a structural function, for instance stabilizing the tertiary structure of nucleoprotein or binding an enzyme to its active site. Chromium deficiency in animals is characterized by impaired glucose tolerance with fasting hyperglycemia, glycosuria, hypercholesterolemia, corneal opacities, and impaired growth. This state can be reversed by giving trivalent chromium (Cr^{3+}) or by much smaller amounts of Cr^{3+} given as an organic complex known as glucose tolerance factor (GTF). This substance has been extracted from a brewer's yeast, *Saccaromyces carlsbergensis*, and has a molecular weight of about 500 daltons. Each molecule contains one atom of chromium in a complex consisting of two nicotinic acid molecules, and one each of glycine, cysteine, and glutamic acid. After the removal of the amino acids (which make the complex water soluble), the di-nicotinato tetra aquo compound is thought to break down the intrachain disulfide bridge in the A chain of the insulin molecule, to effect a connection between the insulin molecule and sulfhdryl groups on the membrane receptor. Thus, the GTF may form a stable bridge between insulin and the membrane receptor.[93]

Studies in elderly diabetics[95] and in children recovering from protein-calorie malnutrition[96-98] have shown that Cr^{3+} administration has been associated with improvement of glucose tolerance. More recently, Jeejeebhoy et al[99] have described an adult patient receiving total parenteral nutrition for more than five years in whom there developed an impairment of glucose tolerance and a peripheral neuropathy that was reversed by chromium administration. It is not known how important chromium is for fetal development. In the rat, inorganic ^{51}Cr crosses the placenta very poorly, but ^{51}Cr-labeled GTF extracted from brewer's yeast crosses readily into the fetus.[92] In man, nothing is known about the placental transport of chromium other than that it occurs. Chromium is present in the liver of the human fetus[19] and the concentration in the whole fetus is said to decrease during pregnancy and after birth.[92] This is perhaps reflected in the falling hair chromium concentrations of young infants.[100] It is perhaps worth noting that because of the prevailing and analytical prob-

lems, reported values from chromium should be regarded as provisional.[101]

CONCLUSION

Current knowledge of trace-element metabolism is increasing rapidly with the application of new techniques. Though trace elements are numerous in the body and act at many levels of metabolism, the effects of deficiencies of some of these elements on fetal and neonatal development are only just beginning to be understood. The preterm infant, because of low body stores, inadequate provision of nutrients in the milk, and immature intestinal function, seems particularly at risk of trace mineral deficiency, and research in this area might be repaid with a worthwhile reduction in morbidity.

(This is part 2 of a two-part article.)

The librarians of the Royal Society of Medicine helped with the location of references. Leonard Strang criticized the manuscript, and Joyce Baldwyn typed the manuscript.

References

1. Underwood EJ: *Trace Elements in Human and Animal Nutrition*, ed 3. New York, Academic Press Inc, 1971.
2. Hart EB, Steenbock H, Waddell J, et al: Iron in nutrition: VII. Copper as a supplement to iron for hemoglobin binding in the rat. *J Biol Chem* 77:797-812, 1928.
3. O'Dell B: Biochemistry and physiology of copper in vertebrates, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 1, pp 391-413.
4. Evans GW: Copper homeostasis in the mammalian system. *Physiol Rev* 53:535-570, 1973.
5. Milne DB, Matrone G: Forms of ceruloplasmin in developing piglets. *Biochim Biophys Acta* 212:43-49, 1970.
6. Osaki S, Johnson DA, Frieden E: The possible significance of the ferrous oxidase activity of ceruloplasmin in normal human serum. *J Biol Chem* 241:2746-2751, 1966.
7. Lardy H: Fifty years ago: Copper as an essential element for iron utilization. *Trends Biochem Sci* 3:93-94, 1978.
8. Lee GR, Williams DM, Cartwright GE: Role of copper in iron metabolism and heme biosynthesis, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 1, pp 373-390.
9. McCosker PJ: Paraphenylene diamine oxidase activity and copper levels in mammalian plasmas. *Nature* 190:887-889, 1961.
10. Evans GW, Wiederanders RE: Blood copper variation amongst species. *Am J Physiol* 213:1183-1185, 1967.
11. Seal US: Vertebrate distribution of ceruloplasmin and sialic acid and the effects of pregnancy. *Comp Biochem Physiol* 13:143-159, 1964.
12. Goodman JR, Dallman PR: Role of copper in iron localization in developing erythrocytes. *Blood* 34:747-753, 1969.
13. Tephly TR, Wagner G, Sedman R, et al: Effects of metals on haem biosynthesis and metabolism. *Fed Proc* 37:35-39, 1978.
14. Wintrobe MM, Cartwright GE, Gubler CJ: Studies of the function and metabolism of copper. *J Nutr* 50:395-419, 1953.
15. Hurley LS: Perinatal effects of trace element deficiencies, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 2, pp 301-314.
16. Kelly WA, Kesterson JW, Carlton WW: Myocardial lesions in the offspring of female rats fed a copper deficient diet. *Exp Mol Pathol* 20:40-56, 1974.
17. Allen KGD, Klevay L: Cholesterolemia and cardiovascular abnormalities in rats caused by copper deficiency. *Atherosclerosis* 29:81-93, 1978.
18. Widdowson EM, Dickerson JWT: Chemical composition of the body, in Comar CL, Bronner F (eds): *Mineral Metabolism*. New York, Academic Press Inc, 1961, vol 2.
19. Widdowson EM, Chan H, Harrison GE, et al: Accumulation of Cu, Zn, Mn, Cr and Co in the human liver before birth. *Biol Neonate* 20:360-367, 1972.
20. Porter H: The particulate half-cystine-rich copper protein of newborn liver: Relationship to metallothionein and subcellular localization in nonmitochondrial particles possibly representing heavy lysosomes. *Biochem Biophys Res Commun* 56:661-668, 1974.
21. Ryden L, Deutsch HF: Preparation and properties of the major copper binding component in human fetal liver: Its identification as metallothionein. *J Biol Chem* 253:519-214, 1978.
22. Shaw JCL: Parenteral nutrition in sick low birth weight infants. *Ped Clin North Am* 20:333-358, 1973.
23. James BE, MacMahon RA: Balance studies of nine elements during complete intravenous feeding of small premature infants. *Austr Paediatr J* 12:154-162, 1976.
24. Bonta BW, Gawron ER, Warshaw JB: Neonatal red cell superoxide dismutase enzyme levels: Possible role as a cellular defense mechanism against pulmonary oxygen toxicity. *Pediat Res* 11:754-757, 1977.
25. Gubler CJ, Lahey ME, Cartwright CE, et al: The transportation of copper in the blood. *J Clin Invest* 32:405-413, 1953.
26. Matsuda I, Pearson T, Holtzman A: Determination of apoceruloplasmin by radioimmunoassay in nutritional copper deficiency, Menkes' kinky hair syndrome, Wilson's disease, and umbilical cord blood. *Pediatr Res* 8:821-824, 1974.
27. Henkin RI, Schulman JD, Schulman CB, et al: Changes in total nondiffusible and diffusible plasma zinc and copper during infancy. *J Pediatr* 82:831-837, 1973.
28. Iyer KS, Lau S-J, Laurie SH, et al: Synthesis of the native copper (II): Transport site of human serum albumin and its copper (II) binding properties. *Biochem J* 169:61-69, 1978.
29. Dixon JW, Sarkar B: Isolation, amino acid sequence and Cu (II)-binding properties of peptide (1-24) of dog serum albumen. *J Biol Chem* 249:5872-5877, 1974.
30. Nassi L, Poggini G, Vecchi C, et al: Zinc, copper and iron in human colostrum and milk. *Minerva Pediatr* 26:832-836, 1974.
31. Hambidge KM: The importance of trace elements in infant nutrition. *Curr Med Res Opin* 4(suppl 1):44-53, 1976.
32. Cavell PA, Widdowson EM: Intakes and excretions of iron, copper and zinc in the neonatal period. *Arch Dis Child* 39:496-501, 1964.
33. Kleinbaum H: Kupferstoffwechselbilanzen bei Säulingen. *Z Kinderheilk* 87:101-115, 1962.
34. Elvehjem CA: The biological significance of copper and its relation to iron metabolism. *Physiol Rev* 15:471-507, 1935.
35. Sturgeon P, Brubacker C: Copper deficiency in infants: A syndrome characterized by hypocupremia, iron deficiency anemia and hypoproteinemia. *Am J Dis Child* 92:254-265, 1956.
36. Schubert WK, Lahey ME: Copper and protein depletion complicating hypoferric anemia in infants. *Pediatrics* 24:710-733, 1959.
37. Zipursky A, Dempsey H, Markowitz H, et al: Studies on copper metabolism: XXIV. Hypocupremia in infancy. *AMA J Dis Child* 96:148-158, 1958.
38. Graham G, Cordano A: Copper deficiency in human subjects, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 1, pp 363-372.
39. Sivasubramanian KN: Zinc and copper changes after neonatal parenteral alimentation. *Lancet* 1:508, 1978.
40. Sivasubramanian KN, Henkin RI: Behavioral and dermatological changes and low serum zinc and copper concentrations in two premature infants after parenteral alimentation. *J Pediatr* 93:847-851, 1978.
41. Fleming CR, Hodges RE, Hurley LS: A prospective study of serum copper and zinc levels in patients receiving total parenteral nutrition. *Am J Clin Nutr* 29:70-77, 1976.
42. Karpel JT, Peden VH: Copper deficiency in long-term parenteral nutrition. *J Pediatr* 80:32-36, 1972.
43. Vilter RWR, Bozian RC, Hess EV, et al: Manifestations of copper deficiency in a patient with systemic sclerosis on intravenous hyperalimentation. *N Engl J Med* 291:188-191, 1974.
44. Dunlap WM, James GW, Hume DM: Anemia and neutropenia caused by copper deficiency. *Ann Intern Med* 80:470-476, 1974.
45. Zidar BL, Shadduck RK, Zeigler Z, et al: Observations on the anemia and neutropenia of human copper deficiency. *Am J Hematol* 3:177-185, 1977.
46. Heller RM, Kirchner SG, O'Neil JA Jr, et al: Skeletal changes of copper deficiency in infants receiving prolonged total parenteral nutrition. *J Pediatr* 92:947-949, 1978.
47. Al-Rashid RA, Spangler J: Neonatal copper deficiency. *N Engl J Med* 285:841-843, 1971.
48. Seely JR, Humphrey GB, Matler BJ: Copper deficiency in a premature infant fed on iron fortified formula. *N Engl J Med* 286:109, 1972.
49. Ashkenazi A, Levin S, Djaldetti M, et al: The syndrome of neonatal copper deficiency. *Pediatrics* 52:525-533, 1973.
50. Griscom NT, Craigh JN, Neuhauser EBD: Systemic bone disease developing in small premature infants. *Pediatrics* 48:883-895, 1971.
51. Sann L, David L, Galy G, et al: Copper deficiency and hypocalcaemic rickets in a small for date infant. *Acta Paediatr Scand* 67:303-307, 1978.
52. Dauncey MJ, Shaw JCL, Urman J: The absorption and retention of magnesium, zinc and copper by low birth weight infants fed pasteurized human breast milk. *Pediatr Res* 11:1033-1039, 1977.
53. Menkes JH, Alter M, Steigleder GK, et al:

A sex linked recessive disorder with retardation of growth, peculiar hair and focal cerebral and cerebellar degeneration. *Pediatrics* 29:764-779, 1962.

54. Williams DM, Alkin CL, Frens DB, et al: Menkes' kinky-hair syndrome: Studies of copper metabolism and long-term copper therapy. *Pediatr Res* 11:823-826, 1977.

55. Danks DM, Stevens BJ, Campbell PE, et al: Menkes' kinky-hair syndrome. *Lancet* 1:1100-1102, 1972.

56. Møllekaer AM: Kinky-hair syndrome. *Acta Paediatr Scand* 63:289-296, 1974.

57. Lott IT, Depaolo R, Schwartz D, et al: Copper metabolism in the steely hair syndrome. *N Engl J Med* 292:197-199, 1975.

58. Daish P, Wheeler EM, Roberts PF, et al: Menkes' syndrome: Report of a patient treated from 21 days of age with parenteral copper. *Arch Dis Child* 53:956-958, 1978.

59. Beratis NG, Price P, La Badie G, et al: ^{64}Cu metabolism in Menkes' and normal cultured skin fibroblasts. *Pediatr Res* 12:699-702, 1978.

60. Wilson SAK: Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. *Brain* 34:295-509, 1912.

61. Scheinberg H, Sternlieb I: Copper toxicity and Wilson's disease, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 1, pp 415-438.

62. Strickland GT, Beckner WM, Mei-Ling L, et al: Turnover studies of copper in homozygotes and heterozygotes of Wilson's disease and controls: Isotope tracer studies with ^{67}Cu. *Clin Sci* 43:605-615, 1972.

63. Evans GW, Dubois RS, Hambidge KM: Wilson's disease: Identification of an abnormal copper binding protein. *Science* 181:1175-1176, 1973.

64. Walshe JM: Brief observations on the management of Wilson's disease. *Proc R Soc Med* 70(suppl 3):1, 1977.

65. Klingberg WG, Prasad AS, Oberleas D: Zinc deficiency following penicillamine therapy, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 1, pp 51-65.

66. Leach RM Jr: Metabolism and function of manganese, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 2, pp 235-247.

67. Hurley LS: Approaches to the study of nutrition in mammalian development. *Fed Proc* 27:193-198, 1968.

68. Erway LC, Fraser AS, Hurley LS: Prevention of congenital otolith defect in pallid mutant mice by manganese supplementation. *Genetics* 67:97-108, 1971.

69. McLeod BE, Robinson MF: Dietary intake of manganese by New Zealand infants during the first six months of life. *Br J Nutr* 27:229-232, 1972.

70. Widdowson EM: Trace elements in human development, in Barltrop D, Burland WL (eds): *Mineral Metabolism in Paediatrics*. Oxford, England, Blackwell Scientific Publications, 1969, pp 85-98.

71. Doisy EA Jr: Micronutrient controls on biosynthesis of clotting proteins and cholesterol, in Hemphill DD (ed): *Trace Substances in Environmental Health*. Columbia, Mo, University of Missouri Press, vol 6, pp 193-199.

72. Schwarz K, Folz CM: Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. *J Am Chem Soc* 79:3292-3293, 1957.

73. Thompson JN, Scott ML: Role of selenium in the nutrition of the chick. *J Nutr* 97:335-342, 1969.

74. Rotruck JT, Pope AL, Ganther ME, et al: Selenium: Biochemical role as a component of glutathione peroxidase. *Science* 179:588-590, 1973.

75. Awasthi YC, Beutler E, Srivastava SK: Purification and properties of human erythrocyte glutathione peroxidase. *J Biol. Chem* 250:5144-5149, 1975.

76. Burk RF, Nishiki K, Lawrence RA, et al: Peroxide removal by selenium dependent and selenium independent glutathione peroxidase in hemoglobin free perfused rat liver. *J Biol Chem* 253:43-46, 1978.

77. Fridovich I: The biology of oxygen radicals. *Science* 201:875-880, 1978.

78. Fridovich I: Superoxide radical and the bactericidal action of phagocytes. *N Engl J Med* 290:624-625, 1974.

79. Gross RT, Bracci R, Rudolph N, et al: Hydrogen peroxide toxicity and detoxification in erythrocytes of newborn infants. *Blood* 29:481-493, 1967.

80. Necheles TF, Boles TA, Allen DM: Erythrocyte glutathione peroxidase deficiency and hemolytic disease of the newborn infant. *J Pediatr* 72:319-324, 1968.

81. Swierczewski E, Demus-Oole AM, Minkowski A: Glutathione peroxidase and catalase in the erythrocytes of premature full-term and hypotrophic infants. *Z Klin Chem* 7:208-209, 1969.

82. Whaun JM, Oski FA: Relation of red cell glutathione peroxidase to neonatal jaundice. *J Pediatr* 76:555-560, 1970.

83. Emerson PM, Mason DY, Cuthbert JE: Erythrocyte glutathione peroxidase content and serum tocopherol levels in newborn infants. *Br J Haematol* 22:667-680, 1972.

84. Glader BE, Conrad ME: Decreased glutathione peroxidase in neonatal erythrocytes: Lack of relation to hydrogen peroxide metabolism. *Pediatr Res* 6:900-904, 1972.

85. Lie-Injo LE, Wong WP, Ng T: Reduced glutathione, glutathione reductase, glutathione peroxidase, and pyruvate kinase in the erythrocytes of human newborns and adults in Malaysia. *Br J Haematol* 25:577-584, 1973.

86. Rudolph N, Wong SL: Selenium and glutathione peroxidase activity in maternal and cord plasma, and red cells. *Pediatr Res* 12:789-792, 1978.

87. Yam J, Lee F, Roberts RJ: Oxygen toxicity: Comparison of lung biochemical responses in neonatal and adult rats. *Pediatr Res* 12:115-119, 1978.

88. Fomon SJ: *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1973.

89. Thorn J, Robertson J, Buss DH, et al: Trace nutrients: Selenium in British food. *Br J Nutr* 39:391-396, 1978.

90. Ricour C, Gros J, Maziére B, et al: Trace elements in children on total parenteral nutrition. *Acta Chir Scand Suppl* 466:22-23, 1976.

91. Lombeck I, Bremer HJ: Primary and secondary disturbances in trace element metabolism connected with genetic disorders. *Nutr Metab* 21:49-64, 1977.

92. Mertz W: Chromium occurrence and function in biological systems. *Physiol Rev* 49:153-239, 1969.

93. Mertz W, Toepfer EW, Roginski EE: Present knowledge of the role of chromium. *Fed Proc* 33:2275-2280, 1974.

94. Anderson RA, Mertz W: Glucose tolerance factor: An essential dietary agent. *Trends Biochem Sci* 2:277-279, 1977.

95. Doisy RJ, Streeten DHP, Freiberg JM, et al: Chromium metabolism in man and biochemical effects, in Prasad AS, Oberleas D (eds): *Trace Elements in Human Health and Disease*. New York, Academic Press Inc, 1976, vol 2, pp 79-104.

96. Gurson GC, Saner G: Effect of chromium on glucose utilization in marasmic protein calorie malnutrition. *Am J Clin Nutr* 24:1313-1319, 1971.

97. Gurson CT, Saner G: Effect of chromium supplementation on growth in marasmic protein-calorie malnutrition. *Am J Clin Nutr* 26:988-991, 1973.

98. Hopkins LL, Ransome-kuti O, Majaj AS: Improvements of impaired carbohydrate metabolism by chromium (III) in malnourished infants. *Am J Clin Nutr* 21:203-211, 1968.

99. Jeejeebhoy KN, Chu RC, Marliss EB, et al: Chromium deficiency, glucose intolerance and neuropathy reversed by chromium supplementation in a patient receiving long-term total parenteral nutrition. *Am J Clin Nutr* 30:531-538, 1977.

100. Hambidge KM, Baum JD: Hair chromium concentrations of human newborn and changes during infancy. *Am J Clin Nutr* 25:376-379, 1972.

101. Mertz W: Trace element nutrition in health and disease: Contribution and problems of analysis. *Clin Chem* 21:468-475, 1975.

102. Ohtake M: Serum zinc and copper levels in healthy Japanese infants. *Tohuku J Exp Med* 123:265-270, 1977.

103. Lubchenko LO, Hansman C, Dressler M, et al: Intrauterine growth as estimated from live born birth weight data at 24 to 42 weeks of gestation. *Pediatrics* 32:793-800, 1963.

104. Hambidge KM, Droegmueller W: Changes in plasma and hair concentrations of zinc, copper, chromium and manganese during pregnancy. *Obstet Gynecol* 44:666-672, 1974.

105. Henkin RI, Marshall JR, Meret S: Maternal fetal metabolism of copper and zinc at term. *Am J Obstet Gynecol* 110:131-143, 1971.

106. Mondorf AW, Mackenrodt G, Halberstadt E: Coeruloplasmin. *Klin Wochenschr* 49:61-70, 1971.

107. Favier M, Yacoub M, Racinet G, et al: Les ion métalliques dans le liquide amniotique au cours du troisième trimestre de la gestation: Relation significative entre la concentration en zinc et le poids foetal. *Rev Fr Gynecol* 67:707-714, 1977.

108. Ohtake M, Tamura T: Serum zinc and copper levels in healthy Japanese children. *Tohuku J Exp Med* 120:99-103, 1976.

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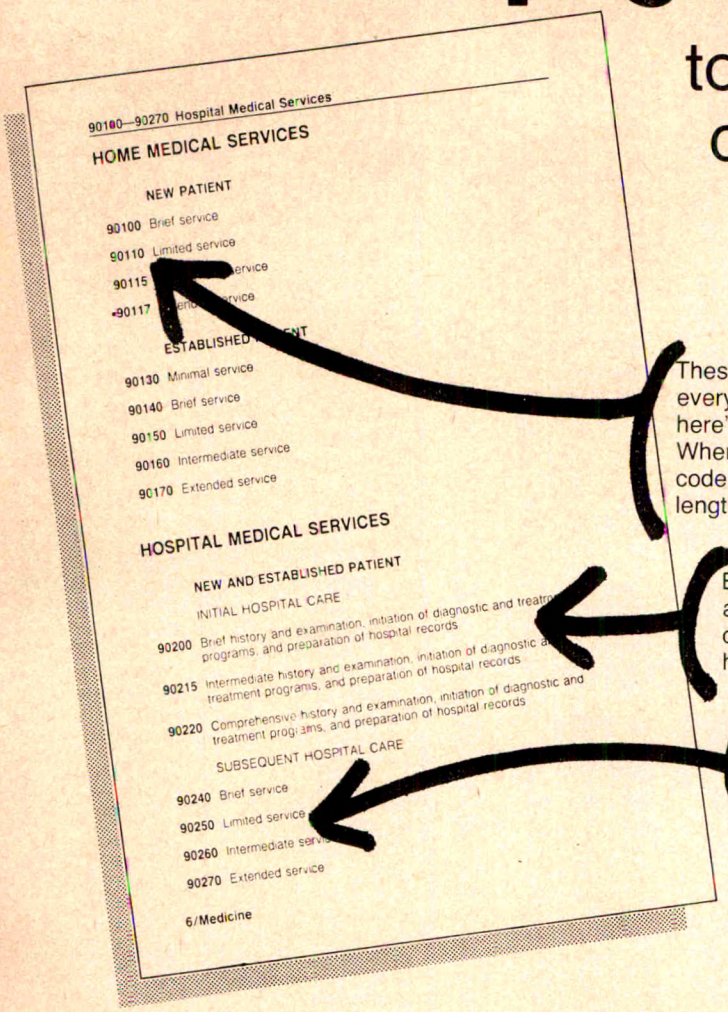

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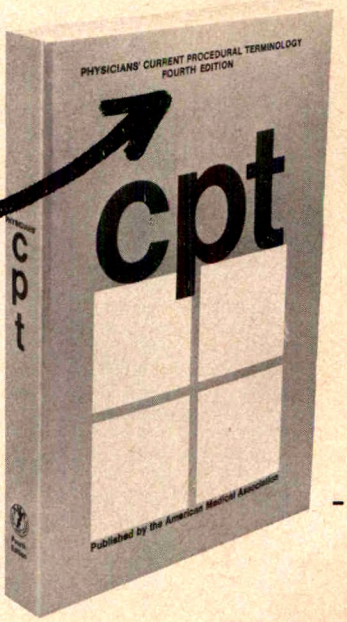

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Radiological Case of the Month

Lionel W. Young, MD; Contributed by Michael V. Severson, MD; Edmund C. Burke, MD; Robert R. Hattery, MD

A week before admission, a boy 3 years 3 months of age was referred to our clinic because his abdomen was large and a huge abdominal mass was palpated by his physician.

On admission, the child's height was 96.5 cm, and he weighed 15.9 kg. He seemed to be in good health although his abdomen was greatly distended. His temperature and blood pressure were normal, as were the results of the rest of the physical examination, excluding the abdomen. Palpation of the abdomen showed a large mass that was soft and nontender; its margins were not discrete. No organs were palpable, and there was no edema.

Hemoglobin level, leukocyte and differential cell counts, urinalysis, and roentgenogram of the chest were normal. The levels of urinary vanillylmandelic acid and homovanillic acid were normal. The serum level of creatinine was 0.45 mg/dL. Values for electrolytes, alkaline phosphatase, SGOT, and SGPT were normal.

An excretory urogram (Fig 1) and abdominal aortograms (Fig 2) were done. Surgical exploration was undertaken.

From the Departments of Pediatrics (Drs Severson and Burke) and Diagnostic Radiology (Dr Hattery), Mayo Clinic and Mayo Foundation, Rochester, Minn.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).

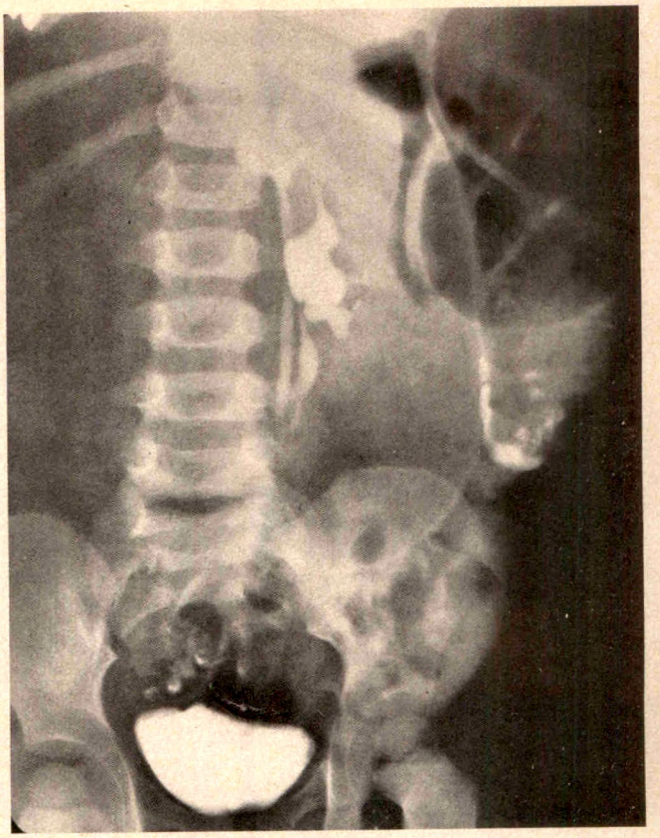

Figure 1.

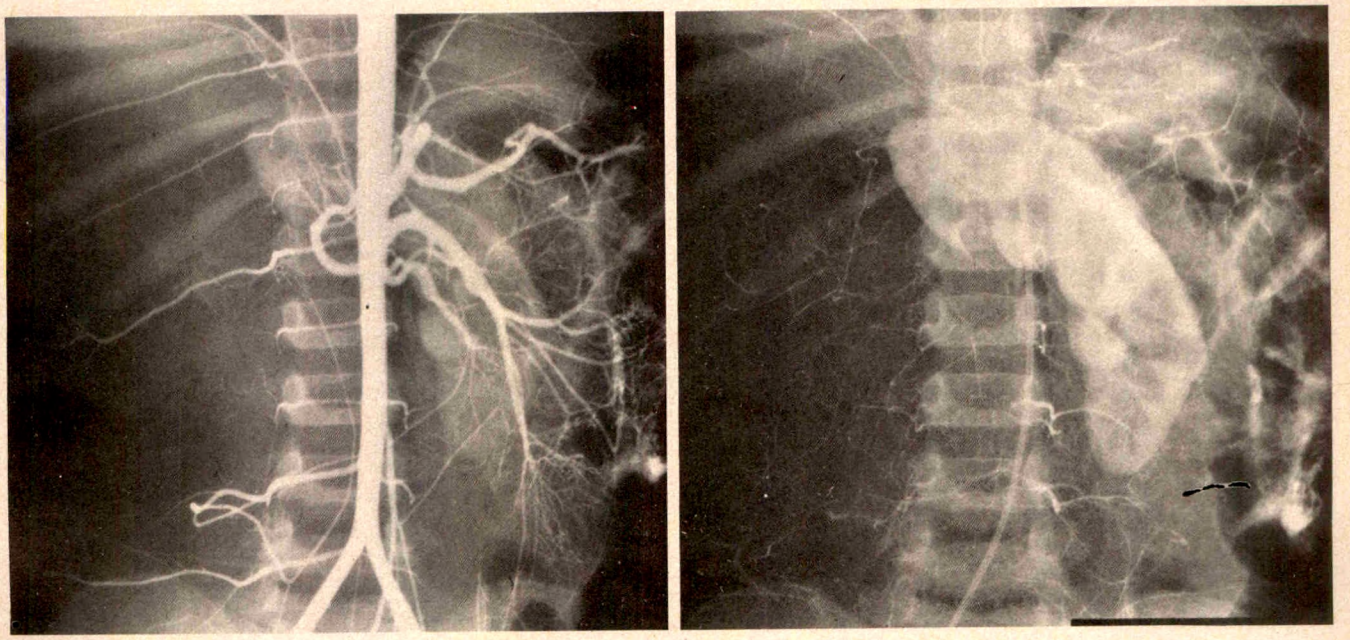

Figure 2.

Denouement and Discussion

Fig 1.—Excretory urogram showing displacement of right kidney superiorly and across midline. Right kidney is displaced but not invaded by mass, and mass does not obstruct ureter.

Fig 2.—Abdominal aortograms showing large tumor in right retroperitoneal space. Left, Major visceral arteries are displaced toward left, and right renal artery is displaced superiorly. Right, Nephrogram phase demonstrates normal renal parenchyma bilaterally.

Fig 3.—Gross lipoma.

Retroperitoneal Lipoma in a Child

Exploration of the right upper quadrant was done transperitoneally through a transverse incision, and a retroperitoneal encapsulated mass was removed. There was no evidence of invasion of adjacent structures, and the kidneys were normal.

The mass weighed 1,870 g (Fig 3). Histologic examination indicated that it was a lipoma. The child has been completely well since the operation five years ago.

Fifteen other instances[1-16] of benign retroperitoneal neoplasms in children have been published, some of which attained incredible size (eg, the heaviest being 2,860 g and the largest being 4,608 cu cm). Histologically, these lesions were essentially lipomas though some had fibromatous or myxomatous elements. Tumors with sarcomatous elements were excluded because of the malignant aspects of such tumors.

Lipoblastomatosis[13] is a separate entity inasmuch as the circumscribed form is generally superficial and the diffuse form is deep, in some instances without continuous capsule and therefore infiltrative. Most patients with lipoblastomatosis were less than 3 years old, and the neoplasms involved the extremities rather than the retroperitoneal area. Chung and Enzinger,[13] however, included two patients with retroperitoneal neoplasms, one patient being a 6-month-old female infant who was well 12 years after its removal.

Irwin et al[16] described a patient with Down's syndrome who died of other causes and whose autopsy disclosed a lipoma weighing 1,750 g. They stated that, whether the neoplasms were removed or not, a slow death usually followed. Their statement is probably erroneous, on the assumption that they were referring to invasive lipoblastomatosis rather than to an encapsulated retroperitoneal lipoma.

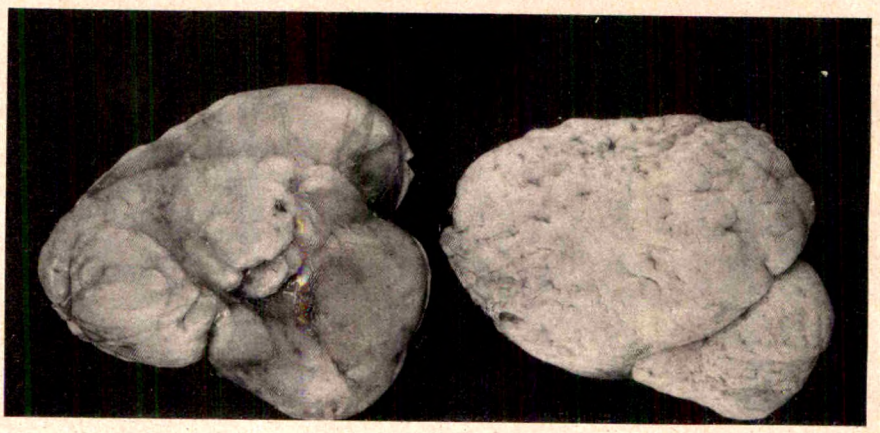

Figure 3.

Current evidence and past experience suggest that a child, well-appearing, free of symptoms, but with a large abdominal mass, should be suspected of having a benign retroperitoneal neoplasm. Such a lesion is surgically curable.

References

1. Lauwers: Lipome de mésentère; ablation, guérison. *Bull Acad R Med Belg* 5:311-316, 1891.
2. Dalziel TK: Specimens: I. A large retroperitoneal lipoma from a child. *Glasgow Med J* 49:372-374, 1898.
3. Bork L: Beitrag zur Kenntniss der Nierenkapselgeschwülste. *Arch Klin Chir* 63:928-947, 1901.
4. Neumann A: Retroperitoneales Lipom der Nierenfettkapsel im Kindersalter. *Arch Klin Chir* 77:411-419, 1905.
5. Kay T: Case of rare pelvic tumor in a child of 4 years. *Glasgow Med J* 70:112-113, 1908.
6. Vautrin: Considerations a propos un cas de lipome retroperitoneale. *Assoc Fran Chir Paris* 21:346-360, 1908.
7. Harrington SW: Subphrenic abscess and acute right empyema secondary to general peritonitis from ruptured appendix; right intrathoracic neurofibroma; abscess of left lobe of liver; retroperitoneal fibromyxolipoma. *Surg Clin North Am* 14:625-638, 1934.
8. Harvard BM: Retroperitoneal lipoma in children: Report of case and review of literature. *J Urol* 70:159-163, 1953.
9. Hastings N, Pollock WF, Snyder W Jr: Retroperitoneal tumors in infants and children. *Arch Surg* 82:950-973, 1961.
10. Seymour EQ, Puckette SE Jr: Retroperitoneal lipoma: A case report in an infant. *J Urol* 100:165-166, 1968.
11. Wolk DP, Schuster KM: Retroperitoneal lipoma in a child. *J Pediatr Surg* 7:343-344, 1972.
12. Gonzales ET Jr, Anderson EE: Retroperitoneal lipoblastic tumors in children. *J Urol* 110:474-475, 1973.
13. Chung EB, Enzinger FM: Benign lipoblastomatosis: An analysis of 35 cases. *Cancer* 34:482-492, 1973.
14. Chown B: Extraperitoneal lipoma in a child. *Am J Dis Child* 57:401-403, 1939.
15. Pinto VC, Mattos AG, Pimenta E, et al: Retroperitoneal myxolipoma: Report of a case in a child 7 years of age. *Pediatrics* 14:11-15, 1954.
16. Irwin GAL, Mehta GB, Neil EE, et al: Massive retroperitoneal lipoma in a mongoloid child: A case report. *Clin Pediatr* 16:195-196, 1977.

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The men and women whose names appear below kindly served as reviewers and referees this past year. The diverse nature of the manuscripts we receive, and their large numbers, means that the Editorial Board must rely on outside help if these manuscripts are to enjoy the sort of critical review that they deserve. So we and our readers thank them one and all.—ED.

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Pulmonary Veno-Occlusive Disease Appearing as Acute, Recurrent Abdominal Pain

Pulmonary hypertension without associated congenital heart defect is uncommon in children. When it occurs, pulmonary hypertension is usually caused by pulmonary arterial involvement and only rarely will primary pulmonary veno-occlusion be found. The symptom in pulmonary veno-occlusive disease is progressive "breathlessness," dyspnea on exertion.[1-3]

We studied a case of pulmonary veno-occlusive disease whose main symptom was severe, recurrent abdominal pain. As abdominal pain is a common childhood complaint, the associated increasing dyspnea was overlooked and the diagnosis of pulmonary veno-occlusive disease not immediately made.

Report of a Case.—A 6-year-old girl was referred for evaluation of recurrent abdominal pain. She had always been healthy and active. For several months she had had episodes of severe abdominal pain after an upper respiratory tract infection. This pain was sudden, severe, and she would turn pale. She complained that her heart pounded and her breathing was rapid. Sometimes she vomited and was exhausted. Her pain came several times daily. Bowel habits were unchanged and a trial of diet and antispasmodics gave no relief. Previous studies included a normal upper and lower gastrointestinal series and ECG. Her EEG was somewhat abnormal, but anticonvulsants did not abolish the abdominal pain.

When evaluated, she appeared small and chronically ill. Examination results were normal except for the cardiac findings. There was a short basal systolic murmur and finely split second sound with accentuation of the second component in the pulmonic area. Blood pressure was 80/60 mm Hg, right arm lying. Chest roentgenogram showed minimal cardiomegaly, pulmonary vascular obstructive changes, and the B lines of Kerley (Fig 1). Electrocardiogram showed moderate right ventricular hypertrophy. She was given digitalis and diuretics. Findings from all laboratory studies were normal. Echocardiogram ruled out a left atrial mass lesion (left atrial diameter, 2.4 cm; left ventricular diameter, 2.1 cm). Cardiac catheterization showed elevated right ventricular and pulmonary artery pressures and a normal pulmonary wedge pressure (Table). During the angiogram, contrast medium filled the main pulmonary artery promptly with a slow run-off. No left atrial filling defect was seen.

On the basis of the clinical, roentgenographic, and catheterization findings, the diagnosis of pulmonary venoocclusive disease was made. An open lung biopsy was performed. She was alert and responsive after the procedure, but 40 minutes later had a cardiac arrest and could not be resuscitated.

The significant findings on gross examination were limited to the thorax. The root of the pulmonary artery was severely dilated, 3 cm in diameter compared to an aortic root of 1.8 cm. The right ventricle was hypertrophied, the left atrium and the mitral valve were normal. Pulmonary vessels protruded from the sectioned surfaces. The microscopic pattern was fairly uniform within all lobes. Hemosiderin-containing alveolar macrophages were clumped focally. There was diffuse though focal alveolar fibrosis. Occasionally there were plasma cells, lymphocytes, and polymorphonuclear leukocytes both within the thickened alveolar septa and also in minute intra-alveolar foci. Occasional bronchiolar mucous gland hyperplasia was noted. The lymphatics were dilated. On hematoxylin-eosin stained sections, there was diffuse but random intimal fibrosis of the pulmonary venous system. Both venules and larger pulmonary veins were involved. Elastic stains showed focal arterialization of the venous system, ie, development of internal and external elastic lamina. The media were thickened in the involved vessels and there was variable narrowing and occlusion with fibrotic tissue. In many vessels, the lumina were multichanneled, suggesting recanalization (Fig 2). Changes in the pulmonary arterial system were limited to medial hypertrophy. As in the previously reported cases, there was no evidence of venous disease in any other organ of the body. The liver was entirely normal.

Comment.—Pulmonary veno-occlusive disease is a rare condition described by Hora in 1934. It occurs mainly in children and young adults and only 31 cases, to our knowledge, have been described in the literature. Both sexes are involved equally. Patients have gradually increasing dyspnea, first on exertion and then continuously. Physical examination and laboratory findings are usually normal until the process progresses to frank cardiac failure, syncope, and death. The ECG may show right ventricular hypertrophy. The chest roentgenogram shows mild to moderate cardiomegaly. Whereas in primary arterial pulmonary hypertension there is a decrease in pulmonary vasculature, the roentgenogram in pulmonary veno-occlusive disease shows a fine, diffuse increase of the interstitial vascular markings. The interlobar fissures may be seen and the B lines of Kerley are often present. Cardiac catheterization shows an elevated pulmonary artery pressure. Pulmonary wedge pressure may be normal or elevated, depending on whether a normal or involved segment of lung is sampled. The pulmonary arteriogram shows large central arteries and a slow run-off because of poor cardiac output.[1-6]

The differential diagnosis includes arterial pulmonary hypertension, mitral stenosis, left atrial myxoma, cor triatriatum, sclerosing mediastinitis, congenital stenosis of the pulmonary veins, and large vessel thromboembolic disease. At this time, the cause is unknown. Thromboembolic and immune complex disease has been postu-

Cardiac Catheterization Data

Site	% O_2	Pressure, mm Hg
Aorta	93	120/63
Pulmonary artery	60	118/55
Right ventricle	55	103/72
Right atrium	56	9/3
Superior vena cava	58	11/1
Left pulmonary artery-wedge	93	16/11 16/13

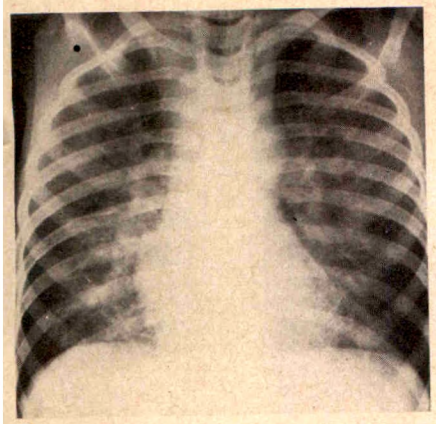

Fig 1.—Chest roentgenogram showing cardiomegaly, venous congestion, and B lines of Kerley.

Fig 2.—Pulmonary vein with almost total luminal obliteration and two small channels suggesting recanalization (hematoxylin-eosin, ×400).

lated and one case had deposits of IgG and complement scattered along the alveolar walls.[7] An infectious agent as the initiating event cannot be ruled out as there is often a preceding viral-type respiratory infection. The process is self-limiting and not all areas of lung are involved. Fresh thrombi or emboli have never been found on any pathologic section.

We presume that in our patient the severe abdominal pain was caused by acute, periodic congestion of the liver with stretching of the capsule. No tachyarrhythmias were ever demonstrated on the ECG. Exertional dyspnea was not considered important because it was overshadowed by the severe abdominal pain.

The course of pulmonary veno-occlusive disease is progressively downhill. Antibiotics, oral anticoagulants, heparin, corticosteroids, and immunosuppressives have all been tried without success.[1-7] The diagnosis of pulmonary veno-occlusive disease is rarely made antemortem. The combination of progressive dyspnea and roentgenographic findings of pulmonary vascular congestion and the B lines of Kerley in a patient with catheterization evidence of pulmonary hypertension should alert the physician to this entity. These children, like all patients with pulmonary hypertension from any cause, tolerate surgical procedures poorly. If the diagnosis can be established with reasonable certainty, lung biopsy should be avoided. Supportive care is all that is available at this time.

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1. Wagenvoort CA, Wagenvoort N (eds): *Pathology of Pulmonary Hypertension*. New York, John Wiley & Sons Inc, 1977, pp 217-231.
2. Wagenvoort CA: Pulmonary veno-occlusive disease. Entity or syndrome? *Chest* 69:82-86, 1976.
3. Shakelford GD, Sacks EJ, Mullins JD, et al: Pulmonary veno-occlusive disease: Case report and review of literature. *Am J Roentgenol* 128:643-648, 1977.
4. Thadani U, Burrow C, Whitaker W, et al: Pulmonary veno-occlusive disease. *Q J Med* 44:133-159, 1975.
5. Rosenthal A, Vawter G, Wagenvoort CA: Intrapulmonary veno-occlusive disease. *Am J Cardiol* 31:78-83, 1973.
6. Scheibel RL, Dedeker KL, Gleason DF, et al: Radiographic and angiographic characteristics of pulmonary veno-occlusive disease. *Radiology* 103:47-51, 1972.
7. Corrin B, Spencer H, Turner-Warwick M, et al: Pulmonary veno-occlusion: An immune complex disease? *Virchow Arch* 364:81-91, 1974.

Cimetidine in Pregnancy: Apparent Transient Liver Impairment in the Newborn

Cimetidine, a potent H_2 receptor antagonist, recently introduced for the treatment of peptic ulcer and other related disorders, has gained widespread use. Most of the current knowledge of its use and effects is based on adult clinical trials. There is a lack of data on its effects in children and infants and virtually none on the human fetus. Animal studies using radioactive labeled cimetidine at doses of 100 mg/kg indicate that this drug crosses the placental barrier and has thus the potential of producing a systemic effect in utero. Elevated transaminase levels have been reported in adults,[1,2] and cholestatic jaundice has been observed in children.[3] This report concerns the finding of liver impairment in an infant born to a mother receiving cimetidine in the last trimester of her pregnancy.

Report of a Case.—This male patient was born to a 39-year-old, gravida 4, para 2, still-birth 1 whose pregnancy was complicated by an exacerbation of her peptic ulcer disease two months prior to delivery. This was treated initially with a mixture of aluminum hydroxide gel and magnesium hydroxide (Maalox) and with belladonna alkaloids with phenobarbital (Donnatal). One month later, she was hospitalized with a bleeding ulcer and started receiving cimetidine (Tagamet), 300 mg four times a day, and a mixture of aminoacetic acid and calcium carbonate (Titralac), 0.84 g every eight hours. At the time of delivery, the mother was receiving the same cimetidine and aminoacetic acid-calcium carbonate regimen in addition to prenatal vitamins and iron supplementation.

Birth was at 37 weeks of gestation by vaginal delivery (breech with forceps extraction). The infant was meconium-stained and had Apgar scores of 2 and 5 at one and five minutes, respectively. Birth weight was 1,676 g. The child was transported to our hospital because of respiratory distress, but this was of short duration. On admission, the infant appeared small for gestational age, with widely split sutures, and a liver palpable 4 cm below the costal margin; the spleen was not palpable. Initial laboratory findings included bilirubin levels of 3.7 mg/dL (total) and 1.5 mg/dL (direct) at six hours of age. Bilirubin levels increased and peaked at 4 days of life at a level of 10 mg/dL (total) with 4.5 mg/dL (direct). The bilirubin elevations and other abnormal liver tests are recorded in the Table.

Blood group incompatibility and congenital infections were ruled out as possible causes of jaundice. Toxoplasmosis titer was negative, as well as the results of viral titers that are presented in the Table. Hepatitis B surface antigen was nonreactive, and the T_4 level was 8.6 μg/dL. Further workup resulted in an α_1-antitrypsin level of 400 mg/dL, a negative urinary metabolic screening, and a normal upper gastrointestinal study.

The initial clinical course was characterized by feeding intolerance, inadequate weight gain, and persistence of jaundice. At 2½ weeks of age, phenobarbital therapy was started at a dose of 4 mg/kg/day as an attempt to induce hepatic function. As the total bilirubin level decreased to 1.2 mg/dL, the drug's use was discontinued after 31 days. At 25 days of age, the patient was discharged at the request of the family, weighing 2.04 kg. Follow-up visits at 30, 48, and 62 days of age showed a progressive decrease in liver size, gradual clearance of the jaundice, and an appropriate weight gain. A liver biopsy, although scheduled, was deferred owing to the clinical improvement of the liver disease.

Comment.—Cimetidine crosses the

Laboratory Values of Liver Function Tests and Viral Titers

Test	Normal Values for Neonates	Values for Patient on Day 1	3	4	12	18	24	30	48	62
Alkaline phosphatase, IU/L	66-217	...	...	46	...	117	150	156	101	...
Bilirubin (total), mg/dL	≤2	3.7	8.8	10	7.1	9.1	6.7	4.8	1.2	0.8
Bilirubin (direct), mg/dL	≤1.5	1.5	3.3	4.5	4.2	4.6	4.1	2.1	...	...
SGOT, IU/L	37-43	...	...	265	118	126	101	88	29	...
SGPT, IU/L	32-38	...	...	115	67	77	65	50	20	...
Cytomegalovirus titers	...	1:64	...	...	...	...	...	...	...	1:8
Rubella titers	...	1:64	...	...	...	...	...	...	...	1:32
Herpes titers	...	1:64	...	...	...	...	...	...	...	1:32

placenta, but its effect on the human fetus and the newborn infant are unknown. In animal studies, no teratologic effects have been identified on the basis of deformities or early development. The effect of cimetidine on the liver has been documented both in animal and clinical studies. Studies in rats and dogs using supratherapeutic dose ranges have demonstrated elevated serum transaminase and alkaline phosphatase levels, with liver biopsy specimens showing centrilobular degenerative changes and inflammatory cell infiltration.[4]

In the early adult human studies, transient elevations in SGOT, SGPT, lactic dehydrogenase, alkaline phosphatase, and bilirubin were recorded and rarely became of any major clinical consequence.[1] Sharpe and Hawkins[2] reported clinically important increases in transaminase levels in four adult patients, two of whom showed mild centrilobular necrosis on liver biopsy specimen. A recent study[3] of children (1 year to 14 years old) treated with cimetidine reported a finding of cholestatic jaundice with elevations of serum bile acids, bilirubin, SGOT, and alkaline phosphatase. The presence of hepatic excretory impairment in our paitent points to a possible contributing effect of cimetidine administration in utero. The progressive elevation in bilirubin from birth to day 4 in our patient may be explained on the basis of removing the placenta as a source of bilirubin elimination.[5,6]

The mechanism by which cimetidine affects hepatic function is unclear. Kinetic studies in man indicate that the drug is primarily excreted by the kidney, 50% to 60% unchanged, and the remainder as conjugates and metabolites, with fecal excretion approximating 10%. The major metabolite is the sulfoxide, accounting for 10% of the urinary excretion.[7] Biliary levels of cimetidine have been reported to be higher than portal or systemic blood levels.[8] This finding sets the potential for a possible interference with hepatic excretory function (eg, hepatic bile acid transport). The immature liver of a fetus and/or premature infant would possibly be more susceptible to a drug causing minor degrees of interference with bile acid transport. The other drugs ingested by the mother have not been associated with liver impairment. The question that surfaces by this case account is whether cimetidine causes hepatic dysfunction in utero and postnatally. This report does no more than suggest a causal relationship, but we believe it may justify the need for carefully monitoring pregnant patients given cimetidine therapy, particularly looking at the outcome of delivery and offspring. Further analysis of cimetidine therapy in pregnancy is warranted to resolve its in utero effect.

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1. Kruss DM, Littman A: Safety of cimetidine. *Gastroenterology* 74:478-483, 1978.

2. Sharpe PC, Hawkins BW: Efficacy and safety of cimetidine: Long-term treatment with cimetidine, in Burland WL, Simkins MA (eds): *Cimetidine, Proceedings of the Second International Symposium on Histamine H_2 Receptor Antagonists*. Amsterdam Excerpta Medica, 1977, pp 358-366.

3. Lilly JR, Hitch DC, Javitt NB: Cimetidine cholestatic jaundice in children. *J Surg Res* 24:384-387, 1978.

4. Leslie GI, Walker TF: A toxicological profile of cimetidine, in Burland WL, Simkins MA (eds): *Cimetidine, Proceedings of the Second International Symposium on Histamine H_2 Receptor Antagonists*. Amsterdam, Excerpta Medica, 1977, pp 24-33.

5. Maisels MJ: Neonatal jaundice, in Avery GB (ed): *Neonatology: Pathophysiology and Management of the Newborn*. Philadelphia, JB Lippincott Co, 1975, pp 335-337.

6. Odell GB, Poland RL, Ostrea EM: Neonatal hyperbilirubinemia, in Klaus MH, Fanaroff AA (eds): *Care of the High Risk Neonate*. Philadelphia, WB Saunders Co, 1975, pp 183-184.

7. Griffiths R, Lee RM, Taylor DC: Kinetics of cimetidine in man and experimental animals, in Burland WL, Simkins MA (eds): *Cimetidine, Proceedings of the Second International Symposium on Histamine H_2 Receptor Antagonists*. Amsterdam, Excerpta Medica, 1977, pp 38-53.

8. Spence RW, Celestin LR, De La Guardia R, et al: Biliary secretion of cimetidine in man, in Burland WL, Simkins MA (eds): *Cimetidine, Proceedings of the Second International Symposium on Histamine H_2 Receptor Antagonists*. Amsterdam, Excerpta Medica, 1977, pp 81-86.

Herpes Simplex Infection After Needle Aspiration of a Lymph Node

Primary infection with herpes simplex virus (HSV) occurs often in childhood. The most common manifestation is gingivostomatitis, while keratoconjunctivitis and skin disease are uncommon.[1-3] Few reports of culturally confirmed, localized, posttraumatic herpes simplex infection during childhood, apparently unrelated to autoinoculation, exist in the literature.[3-5] We report a traumatic HSV skin infection occurring three days after needle aspiration of a presumed bacterial cervical adenitis.

Report of a Case.—An 18-month-old, previously healthy boy developed diffuse swelling of the right side of the neck one day before admission. The past medical history included a unilateral otitis media two months prior to admission. He had no history of herpetic infection nor did any members of his immediate family. Physical examination revealed a listless, febrile (39.2 °C) toddler with a firm, tender mass obscuring the angle of the mandible and extending over the sternocleidomastoid muscle. The overlying skin was hot and erythematous. The rest of the physical examination was unremarkable. The WBC count was 19,500/cu mm, with a shift to the left. Blood cultures were sterile. He was initially treated with a cephalosporin, without improvement. On the third day of hospitalization, a needle aspirate from the mass revealed small, Gram-negative rods

Crop of vesicles that appeared at site of cervical lymph node aspiration.

resembling *Haemophilus influenzae*, but the bacterial culture was sterile. He was given ampicillin sodium, and three days later, when the patient was improving, a vesicular eruption was noted at the aspiration site (Figure). Scrapings from the base of the vesicles revealed numerous multinucleated giant cells. Herpes simplex virus was isolated from the vesicle fluid in human embryonic kidney cells. The virus was identified as type 1 by a direct immunofluorescence technique. The adenopathy resolved uneventfully with treatment. The complement fixation (CF) titer to HSV was 1:16, and the indirect hemagglutination titer to type 1 HSV was 1:4,096 one month after infection.

Comment.—The present case represents an unusual example of traumatic herpes infection that may be encountered in clinical practice. Since two thirds of herpetic infections are asymptomatic[3] and a history of previous infection or exposure is often absent, it is difficult to differentiate between primary infection and recurrence. In addition, CF antibody titer to HSV can be low at the initial phase of a recurrence.[3] Without an acute serum specimen or previous history of disease, we were unable to determine if this patient's disease was a primary infection or reactivation of latent virus.

Latent infection can be activated by a variety of factors such as fever, emotional reactions, upper respiratory infection, pneumococcal or meningococcal infection, excessive exposure to sunlight, and local trauma.[2,3,6] Examples of local trauma resulting in disease include herpes labialis after blow-out fractures of the orbit[7]; herpetic whitlow after trauma to fingers[3,8]; cutaneous eruptions after trigeminal nerve rhizotomy,[6] shaving,[3] smallpox vaccination,[5] intramuscular injections,[9] or direct trauma from falling[3]; herpes gladiatorum in wrestlers[2]; and tracheal ulcers after intubation.[10]

The rapid response to ampicillin and the Gram-negative rods seen on Gram's stain suggest a bacterial etiology for the cervical adenitis. However, a herpetic etiology is also possible and could not be excluded with the available information.

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James E. Ford III, MD, and Newton Coker, MD, referred the patient. Serologic and virologic studies were provided by Maj George Michels at the Virology Laboratory, Dwight David Eisenhower Army Medical Center, Fort Gordon, Ga. Tina Teston provided secretarial assistance.

Nonproprietary Name and Trademarks of Drug

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*

1. Juretic M: Natural history of herpetic infection. *Helv Paediatr Acta* 4:356-368, 1966.
2. Haynes RE: The spectrum of herpes simplex virus infections in children. *S Med J* 69:1069-1078, 1976.
3. Juel-Jensen BE, MacCallum FO: *Herpes Simplex, Varicella and Zoster: Clinical Manifestations and Treatment.* Philadelphia, JB Lippincott Co, 1972, pp 32-76.
4. Findlay GM, MacCallum FO: Recurrent traumatic herpes. *Lancet* 1:259-261, 1940.
5. Warren WS, Salratore MA: *Herpesvirus hominis* infection at a smallpox vaccination site. *JAMA* 205:931-933, 1968.
6. Carton CA, Kilbourne ED: Activation of latent herpes simplex by trigeminal sensory root section. *N Engl J Med* 246:172-176, 1952.
7. Hoyt CS, Billson FA: Herpex simplex infection after blow-out fractures. *Lancet* 2:1364, 1976.
8. Stern H, Elek SD, Millar DM, et al: Herpetic whitlow: A form of cross-infection in hospitals. *Lancet* 2:871-874, 1959.
9. Slavin HB, Ferguson JJ Jr: Zoster-like eruptions caused by the virus of herpes simplex. *Am J Med* 8:456-467, 1950.
10. Nash G: Necrotizing tracheobronchitis and bronchopneumonia consistent with herpetic infection. *Hum Pathol* 3:283-291, 1972.

Severe Neonatal Chlamydial Pneumonitis

Chlamydia are bacteria-like obligatory intracellular parasites. Although they were considered once to be large viruses, they differ from the viruses in having two nucleic acids and in having a discrete cell wall. They do resemble viruses only in the obligatory intracellular nature of their parasitism.[1,2]

A number of human diseases are caused by *Chlamydia*. Recent studies have shown that chlamydial infection in the newborn is associated with a pneumonia syndrome that is characterized by an afebrile course, chronic diffuse lung involvement, tachypnea, and elevated serum IgG and IgM levels.[3-5]

In the 2-week-old infant with severe pneumonitis who is to be described, *C trachomatis* was isolated from tracheal aspirates as well as from her mother's cervix.

Report of a Case.—A 4,100-g term female infant was born to a 30-year-old mother, after a normal pregnancy, labor, and delivery. There was no maternal history of conjunctivitis, or of respiratory or genital infection during pregnancy. The infant was discharged from the nursery after four days. A day later, the infant was found to have a temperature of 39 °C and, two days later though her temperature had returned to normal she began to feed poorly and a mild cough developed. For the next six days, progressive tachypnea and cyanosis were noted by the parents.

On admission to the pediatric intensive care unit, the infant was cyanotic, with respirations of 120/min and severe chest retractions but she was afebrile. Diffuse crepitations and diminished breath sounds were audible in both lungs. The remainder of the physical examination was unremarkable.

Chest roentgenogram disclosed bilateral diffuse interstitial infiltrates (Fig 1). Laboratory tests included a hemoglobin level of 9.6 g/dL, a WBC count of 14,000/cu mm, with 20% neutrophils, 20% band forms, 50% lymphocytes, 5% monocytes, and 5% eosinophils. There were no findings indicating hemolysis. Blood loss could be attributed to withdrawal of blood for investigations. Serum immunoglobulins were as follows: IgA, 20 mg/dL (normal, 4 to 35); IgM, 280 mg/dL (normal, 20 to 80); IgG, 980 mg/dL (normal, 350 to 1,000). The laboratory values for blood urea, creatinine, calcium, uric acid, and urinalysis were within normal limits. Arterial blood sample on admission showed a pH of 7.23, a $Paco_2$ of 65 mm Hg, and a PaO_2 of 40 mm Hg.

The infant was intubated and mechanically ventilated for the next five days. Subsequently, a gradual improvement in the clinical as well as in the arterial blood gas analysis was noted and the infant was extubated on the sixth hospital day, at which time the chest roentgenogram showed some clearing of both lung fields. The infant was given supplemental oxygen via oxyhood for the next two weeks. A week after extubation, arterial blood sample revealed a pH of 7.38, a $Paco_2$ of 44 mm Hg, and a Pao_2 of 88 mm Hg while on

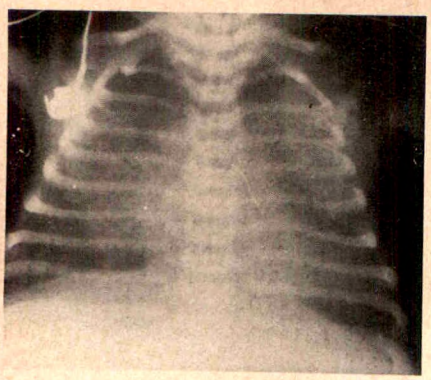

Fig 1.—Chest roentgenogram, obtained on first hospital day, showing severe bilateral interstitial pneumonitis.

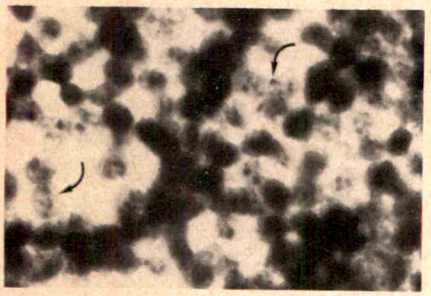

Fig 2.—Two McCoy cell populations are demonstrated (Giemsa stain, ×450). Dark homogenous-appearing cells are unaffected McCoy cells. Light granular-appearing cells contain typical inclusion bodies of *Chlamydia trachomatis* (arrows).

fraction of inspired oxygen of 0.3.

Tracheal aspirates, which were studied for bacteria and viruses (cytomegalovirus, respiratory syncytial virus, rubella, influenza, parainfluenza) were negative. Methenamine silver nitrate stain of the aspirated material for *Pneumocystis carinii* was also negative. Cultures for *C trachomatis* were positive.

No antimicrobial therapy was administered and the patient was discharged on the 21st hospital day after having recovered completely from the pneumonitis. Chest roentgenogram as well as arterial blood gases on the day of discharge were within normal limits.

Patient Sampling and Specimen Processing.—We obtained tracheal aspirates from the patient, under direct laryngoscopy, by a No. 5 F feeding tube. Approximately 0.3 mL were aspirated and then suspended in 3 mL of collecting medium consisting of sucrose-phosphate medium with 5 mγ/mL of streptomycin and 25 units/mL of nystatin. Cultures from the cervical discharge of the infant's mother were obtained under direct vision with a cotton-tipped applicator and were then immersed and wrung out in the collecting medium.

Bacteriologic cultures were processed in the laboratory according to standard procedures for aerobic bacteria. In an attempt to isolate viruses, tracheal aspirates were inoculated onto a primary human kidney (embryo) and African green monkey kidney cell lines and followed up for three weeks. For isolation of *Chlamydia*, cytochalasin B-pretreated McCoy cells were used according to the method of Sompolinsky and Richmond.[6] Isolates that formed iodine-staining cytoplasmatic inclusion bodies were considered to be strains of *C trachomatis*. A two-dimensional immunoelectrophoresis, which was used according to the method of Caldwell et al,[7] also confirmed that the isolates are of the human strain. The cultures were stained by Giemsa for microscopic examination (Fig 2).

Comment.—Interstitial pneumonitis in early infancy is a common clinical problem for which viruses are often incriminated. Beem and Saxon[4] have shown the association between the presence of nasopharyngeal *C trachomatis* and a pneumonia syndrome of infancy. *Chlamydia trachomatis*, the etiologic agent of trachoma,[8] inclusion conjunctivitis,[9] and some of the nongonococcal urethritis,[10] causes pneumonitis in infants that is manifested by nasal obstruction and discharge, staccato cough, tachypnea, and afebrile course, and elevated serum levels of IgG and IgM. Six weeks was the typical age at diagnosis and inclusion conjunctivitis was diagnosed in only 50% of the infants in the patients studied by Beem and Saxon.[4]

Frommell and associates[11] reported a case of *C pneumonitis* in which the patient underwent open lung biopsy, which yielded positive cultures for *Chlamydia* and cytomegalovirus. What is to our knowledge the first pure chlamydial pneumonitis proved by biopsy specimen, of a 5-week-old boy, has been described recently by Arth et al.[12]

Although all previous reports of chlamydial pneumonitis have not been associated with severe morbidity or mortality in infants, our patient was critically ill.

Erythromycin and sulfonamides are currently the most acceptable antimicrobial agents in this pediatric age group.[13] In our case, antimicrobial therapy was not started since the clinical condition, the laboratory findings, and the chest roentgenogram suggested viral pneumonitis. *Chlamydia trachomatis* was isolated on the eighth day of the illness, while the infant was already recovering; hence, specific treatment was not considered essential.

Studies performed by Chandler et al[14,15] and by Shachter and his colleagues,[5] showed that the range of the chlamydial carrier state in pregnant women is between 5% and 13%; thus, a substantial proportion of neonates are at risk. Chandler and associates[14] showed that 50% of the neonates born to women who carry the infection acquired inclusion conjunctivitis. It was also estimated[5] that the incidence of neonatal chlamydial pneumonitis is three to four per 1,000 live births. This relatively high incidence suggests that serious consideration should be given to screening of pregnant women routinely, isolation of *Chlamydia*, and effectively treating them prior to delivery.

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1. Moulder JW: *The Psittacosis Group as Bacteria*. New York, John Wiley & Sons Inc, 1964.
2. Moulder JW: The relation of the psittacosis group *(Chlamydia)* to bacteria and viruses. *Annu Rev Microbiol* 20:107-130, 1966.
3. Shachter J, Lum L, Gooding CA, et al: Pneumonitis following inclusion blennorrhoea. *J Pediatr* 87:779-780, 1975.
4. Beem MO, Saxon EM: Respiratory-tract colonization and a distinctive pneumonia syndrome in infants infected with *Chlamydia trachomatis*. *N Engl J Med* 296:306-310, 1977.
5. Shachter J: Chlamydial infections. *N Engl J Med* 298:428-435, 1978.
6. Sompolinsky D, Richmond S: Growth of *Chlamydia trachomatis* in McCoy cells treated with Cytochalasin. *Appl Microbiol* 28:912-914, 1974.
7. Caldwell HD, Choukuo C, Kenny GE: Antigenic analysis of *Chlamydia* by two-dimensional immunoelectrophoresis. *J Immunol* 115:969-975, 1975.
8. Tang FF, Chang HL, Huang YT, et al: Studies on the etiology of trachoma with special reference to isolation of the virus in chick embryo. *Chin Med J* [*Engl*] 1:902-905, 1959.
9. Jones BR, Collier LH, Smith LH: Isolation of virus from inclusion blennorrhea. *Lancet* 1:902-905, 1959.
10. Holmes KK, Handsfield HH, Wang SP, et al: Etiology of nongonococcal urethritis. *N Engl J Med* 292:1199-1205, 1975.
11. Frommell GT, Bruhn FW, Schwartzman JD: Isolation of *Chlamydia trachomatis* from infant lung tissue. *N Engl J Med* 296:1150-1152, 1977.
12. Arth C, von Schmidt B, Grossman M, et al: Chlamydial pneumonitis. *J Pediatr* 93:447-449, 1978.
13. Beem MO, Saxon EM: Uncertainties in the

treatment of chlamydial infections in infants. *N Engl J Med* 296:1124, 1977.

14. Chandler JW, Alexander ER, Pheiffer TA, et al: Ophthalmia neonatorum associated with maternal chlamydial infections. *Trans Am Acad Ophthalmol Otolaryngol* 83:203, 1977.

15. Alexander ER, Chandler J, Pheiffer T, et al: Prospective study of perinatal *Chlamydia trachomatis* infections, in Holmes KK, Hobson D (eds): Washington, DC, American Society for Microbiology, 1977, pp 148-152.

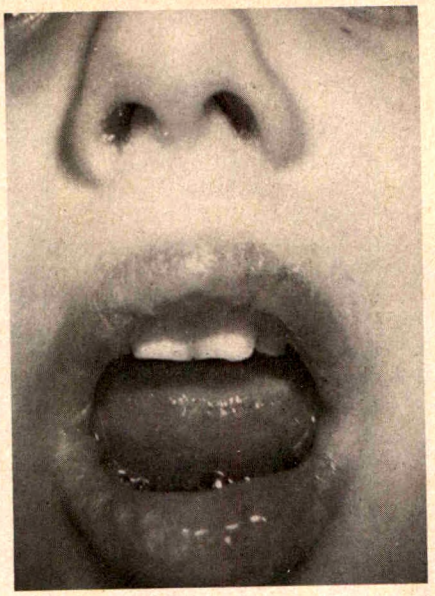
Acute Glossitis and Septicemia Owing to *Haemophilus influenzae* Type B

Acute bacterial glossitis occurs infrequently, judging by the lack of reported cases in the English literature. *Pseudomonas* sp and hemolytic streptococci have been implicated as causative agents of suppurative parenchymatous glossitis.[1] Two cases of acute glossitis owing to *Haemophilus influenzae* type B have been reported, both of them within the past three years.[2,3] We report another case of *H influenzae* type B glossitis to further promote awareness and recognition of this disease.

Report of a Case.—This 4-year-old boy complained of a swollen and painful tongue. He was well until the evening prior to consultation when he complained of a vague discomfort of the tongue. Inspection of the child's mouth by his father did not yield any unusual findings. The child's buccal cavity was sprayed with a mouthwash and he was put to bed. Early the next morning, the patient woke up complaining of increased lingual pain. Swallowing was difficult and the child was drooling. Swelling of the tongue was noted by his parents. The swelling increased during the next three hours, so the child was taken to the emergency room.

On arrival, he appeared moderately ill, uncomfortable, and anxious. He had a temperature of 40.3 °C. He was drooling and refused to talk. His mouth was partially open. His tongue was erythematous, swollen, and tender, almost filling the anterior oral cavity (Figure). The swelling was diffuse but was most prominent in the anterior portion. There was no evidence of injury to the tongue. No associated cervical adenitis was noted. The rest of the physical examination was unremarkable.

Roentgenograms of the soft tissues of the neck showed a large tongue; otherwise, the upper airway showed no abnormalities. The chest roentgenogram was clear. He had a WBC count of 8,900/cu mm, with 80% neutrophils, 9% band forms, and 11% lymphocytes. A diagnosis of acute glossitis was made. A blood culture was done, and the child was given oral oxacillin sodium after an initial intramuscular dose. He was discharged to go home, with instruction to return in eight hours for reevaluation.



Partially open mouth, swollen tongue, and drooling evident on examination.

On return, the oral findings were unchanged. The patient and his parents, however, claimed that he was better. His temperature was 38.5 °C. Continued management of his condition on an outpatient basis was advised. About 24 hours after the initial examination, β-lactamase-negative *H influenzae* type B was isolated from the blood. The patient was recalled and admitted to the hospital for intravenous (IV) ampicillin sodium therapy. He was afebrile and had less pain of the tongue. A repeated blood culture prior to ampicillin therapy also had β-lactamase-negative *H influenzae* type B growth.

One day after starting ampicillin therapy, the patient was afebrile, happy, conversant, and able to tolerate solid food. The lingual swelling had greatly regressed. After completing three days of IV treatment, the patient was sent home with instructions to take oral ampicillin trihydrate for seven more days. The tongue appeared normal. Reevaluation of the patient's condition one month after discharge showed complete resolution of the glossitis.

Comment.—Cellulitis is the most common form of soft-tissue infection caused by *H influenzae* type B. About two thirds of the cases involve the cheeks; approximately 80% are septicemic.[4,5] In 1976, Granoff and Nankervis[2] observed a child, with *H influenzae* type B facial cellulitis, who had diffuse swelling of the tongue and uvula. Subsequently, Edwards and Reynolds[3] described a child with bacteremia owing to *H influenzae* type B in whom swelling of the tongue was the distinctive initial manifestation. Our observation of yet another case of acute swelling of the tongue and septicemia owing to *H influenzae* type B suggests that this organism has an important role in the causation of acute glossitis.

The initial management of our patient's condition reflects the dearth of epidemiologic data on acute bacterial glossitis. The choice of oxacillin for the initial therapy was based on the presumption that the most likely etiologic agent was a Gram-positive microorganism, possibly *Staphylococcus aureus*, or one of the penicillin-sensitive bacteria that comprise the normal oral flora. After the beginning of oxacillin therapy, an apparent clinical improvement occurred in spite of a persistent *H influenzae* bacteremia. This falsely reassuring clinical response could conceivably lead to a delay in starting specific antibiotic therapy and thus could promote metastatic seeding of the meninges, the joints, or other organs. Our experience, as well as that of others, dictate that an *H influenzae* type B infection should be considered in a febrile child who has acute swelling of the tongue. The initial antibiotic therapy of acute glossitis should include drugs effective against *H influenzae*.

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Nonproprietary Names and Trademarks of Drugs

Ampicillin trihydrate—*Alpen, Amcill, Polycillin, Principen.*

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*

1. Chandra T, Prakash A: Suppurative parenchymatous glossitis. *Br J Surg* 52:234-235, 1965.

2. Granoff DM, Nankervis GA: Cellulitis due to *Haemophilus influenzae* type B: Antigenemia and antibody responses. *Am J Dis Child* 130:1211-1214, 1976.

3. Edwards MS, Reynolds GES: Acute glossitis due to *Hemophilus influenzae* type B. *J Pediatr* 93:532-533, 1978.

4. Goetz JP, Tafari N, Boxerbaum B: Needle aspiration in *Hemophilus influenzae* type B cellulitis. *Pediatrics* 54:504-506, 1974.

5. Nelson JD: An hypothesis on the pathogenesis of *Hemophilus influenzae* buccal cellulitis. *J Pediatr* 88:709-710, 1976.

Books

Prenatal Diagnosis of Genetic Disease, by D. C. Siggers, $9, 69 pp, 17 illus, London, Blackwell Scientific Publications, 1978.

This is a thin paperback with a total of 69 pages, of which 44 are text and the remainder are taken up by a list of genetic centers in Britain and the index. As the author states in his preface, the book is intended for postgraduate students in obstetrics, pediatrics, and general practice as well as for medical students, midwives, and pediatric nurses. It is oriented for use in the United Kingdom, but may be of interest to the aforementioned groups elsewhere. It would be particularly useful for the obstetrician who wants a succinct, clearly written review of current aspects of that nagging problem of prenatal diagnosis. The illustrations are good, especially the diagram that shows the risks of trisomy 21 at each year of maternal age from 34 to 41 with the use of Hook's up-to-date data. It is too elementary for medical students, who will have had much more detail in their courses in human genetics.

In addition, Dr Siggers' book provides us with a "slice of life," a snapshot of the situation in prenatal diagnosis in the late 1970s with laboratories for prenatal diagnosis desperately trying to accommodate increasing service loads. The first diagram in the book graphically illustrates the 150-fold increase in service load between 1971 and 1977 at a British cytogenetics unit.

It is unfortunate that the book is quite expensive. Perhaps in a second edition the lists of genetic centers could be left out, since these are already available in the National Foundation's international directory.

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Surgical Management of Juvenile Chronic Polyarthritis, by G. P. Arden, 281 pp, $32.25, New York, Grune & Stratton Inc, 1979.

This book comes from the group associated with the Juvenile Rheumatism Unit at Taplow, Buckinghamshire, England. This unit, founded by Prof E. G. L. Bywaters and soon joined by Barbara Ansell, was a major source of training for many pediatric rheumatologists around the world, and provided care for hundreds of children with arthritis.

The first chapter by Ansell presents a brief and excellent overview of juvenile rheumatoid arthritis (JRA), including the recent attempts in the United States, England, and Europe to reclassify these diseases as they appear in children. The development of subclassification in JRA is of value because with it one would be able to better define the course and progression of the disease as it occurs in an individual child. Unfortunately, this theme was not carried out fully in the chapters on surgery. For example, in the chapter on synovectomy of the knee, there was an initial description of the patients undergoing synovectomy based on whether or not they had sero positive and sero negative JRA of polyarticular and pauciarticular types. But then the author used the term *generalized,* a classification not used initially. He also describes his results in patients with sero positive JRA age 16 to 21 years. However, JRA has been defined as occurring in patients younger than 16 years. Occasionally, the captions under the generally good illustrations do not provide enough information, such as the age or sero positivity of the patient involved.

I cannot agree with Professor Bywaters when, at one point in an otherwise well-illustrated chapter on the pathology of JRA, he states that "in monarticular arthritis . . . a synovial biopsy is almost always necessary, certainly after one month's duration." This indication is not recognized by most pediatric rheumatologists in the United States and I doubt the necessity for such frequency. We are dealing with a condition that involves less than 10% of all the children we see in the usual pediatric arthritis clinic; in half of them, it will resolve within five years (frequently within one year). Careful clinical follow-up should precede any requirements for biopsy. Many other diseases with monarticular onset can be generally eliminated because of their rarity, geographic area, and by clinical and laboratory studies. These, as presented by Professor Bywaters, are sarcoidosis, thorn synovitis, fungal lesions, tuberculosis, other infectious arthritis, pigmented villonodular synovitis, scleroderma, and lupus erythematosus. These zebras may be present, but the pounding hoofbeats are 99% monarticular JRA.

The description by G. P. Arden of total joint replacement is a fascinating assessment of a long and careful experience in these children. This chapter should be of particular interest to both the rheumatologist taking care of these children and to the orthopedist who will be called in to do these procedures. There is good practical information for both.

Harrison's chapter on hand deformities and their correction by splinting and surgery with good descriptions of the operative and nonoperative techniques for maintaining and restoring hand function is of value to the reader. A more detailed description of rehabilitation techniques and the prosthetic devices used for correction and prevention of deformities is presented by Ansell. The disturbing frequency of loss of vision due to the chronic iridocyclitis seen most frequently in those children with pauciarticular disease is discussed in detail by Smiley and Kanski. Their excellent results with the new technique of lensectomy are described in detail and represent an exciting development in a condition heretofore difficult to treat.

Professor Bywaters has provided us not only with the general pathology of juvenile arthritis and some of its mimics but also, with Mr Arden, gives a detailed description of tissue reaction. Most of this chapter is devoted to a description of the failures of prosthesis from the mechanical point of view as well as from infection and allergic and toxic reactions to the materials used.

This slim volume contains a wealth of information of value to the pediatric rheumatologist, orthopedist, ophthalmologist, and pathologist involved in the care of children with juvenile arthritis. It does not provide enough information on therapy for the pediatrician who might have one or two patients with JRA in his practice.

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Letters to the Editor

Marden-Walker Syndrome

Sir.—The interesting article entitled "Zollinger-Ellison Syndrome With Marden-Walker Syndrome" (JOURNAL 133:735-738, 1979) states that this is the fifth reported case of the Marden-Walker syndrome. However, it is the sixth, as in 1971 we published a case.[1]

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1. Fitch N, Karpati G, Pinsky L: Congenital blepharophimosis, joint contractures, and muscular hypotonia. *Neurology* 21:1214-1220, 1971.

Idiopathic Thrombocytopenic Purpura (ITP)

Sir.—I read with interest the article by Movassaghi et al entitled "Antiplatelet Antibodies in Childhood Idiopathic Thrombocytopenic Purpura" (JOURNAL 133:257-259, 1979). However, I cannot agree with their conclusion that platelet antibody usually disappears with recovery from thrombocytopenia in childhood ITP. We have already shown in three chronic and five acute cases of childhood ITP that have been in remission for up to six years that mean platelet survival is shorter with platelet opsonization in five cases (in whom it could be determined).[1,2]

The study has been extended to include 14 children with ITP (six chronic and eight acute) in remission, and again, severe reduction in platelet survival (mean, 4.0 days, which is shorter than in previous reports[1,2]) with platelet opsonization was shown in every case. The antiplatelet antibodies shown by the Handin and Stossel method[3] related to acute phase and remission of 49 childhood ITP cases, and their specificity to IgG will be reported.[4]

Our conclusions from these studies are as follows: antiplatelet antibodies are not only present in the acute phase, but can also be shown in remission in acute and in chronic childhood ITP cases. These antibodies are only in the IgG fraction, as in adult ITP, and are specific for platelets. The pathogenesis of ITP in childhood is not different from that in adult ITP. Since the platelet antibodies do not disappear from the serum during the remission stage, the shorter platelet survival is easily understood in acute and chronic ITP in remission.

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1. Özsoylu Ş, Allahverdi H, Lâleli Y: Platelet survival in cases of idiopathic thrombocytopenic purpura (ITP) in remission, in *Platelets, Recent Advances in Basic Research and Clinical Aspects*, publication 357. Excerpta Medica International Congress Series, Amsterdam, Excerpta Medica, 1974, pp 496-498.

2. Özsoylu Ş, Allahverdi H, Lâleli Y: Platelet survival in childhood idiopathic thrombocytopenic purpura in remission. *J Pediatr* 89:388-390, 1976.

3. Handin RI, Stossel TP: Phagocytosis of antibody coated platelets by human granulocytes. *N Engl J Med* 290:989-993, 1974.

4. Özturk M, Özsoylu Ş, Lâleli Y: Antiplatelet antibodies in childhood idiopathic thrombocytopenic purpura (ITP): Its relation to relapse and remission and specificity to IgG. *Pediatrics*, to be published.

Diabetes Mellitus, Hashimoto's Thyroiditis, and Juvenile Rheumatoid Arthritis

Sir.—We read with interest the report of Collen et al that detailed a case of primary ovarian failure, juvenile rheumatoid arthritis (JRA), and vitiligo (JOURNAL 133:598-600, 1979). We, too, have studied a patient with JRA and an autoimmune polyendocrinopathy.

Report of a Case.—A 15-year-old girl with chronic eczema had insulin-dependent diabetes mellitus (DM) at age 6 years, euthyroid goiter at age 9 years, and debilitating polyarticular JRA with subcutaneous nodules at age 12 years. There was a family history of DM and goiter in the mother and the maternal relatives. After therapy with thyroid and gold, the goiter regressed and the arthritis improved.

Laboratory tests performed at age 13 years showed the following levels: fasting blood glucose, 208 mg/dL; urinalysis, 4 + for glucose, negative acetone, and protein; sedimentation rate, 33 mm/min; VDRL, negative; antinuclear antibody, 1:32, 768; rheumatoid factor, 1:640; antiextractable nuclear antigen, negative; anti-DNA, 27% (normal, < 30%); serum DNA, negative; C_3, 240 mg/dL (normal, 85 to 225 mg/dL); C_4, 57 mg/dL (normal, 20 to 40 mg/dL); total protein, 8.4 g/dL; albumin/globulin ratio, 0.9; γ globulin, 34.2%; IgG, 2,130 μg/dL (normal, 900 to 1,500 μg/dL); IgM, 126 μg/dL (normal, 70 to 280 μg/dL); IgA, 110 μg/dL (normal, 90 to 450 μg/dL); roentgenograms of wrists, bony changes compatible with JRA; tetraiodothyronine, 10.0 μg/dL; antithyroglobulin antibody, 1:68, antimicrosomal antibody, 1:7,000; cortisol baseline, 7.4 μg/dL; cortisol postadrenocorticotropic hormone stimulation, 27.7 μg/dL; antiadrenal antibody, negative; serum B_{12} and peripheral smear, normal; antiparietal cell antibody, negative; and, histocompatibility antigen typing, A28, A9, B27, B7, Cw2.

Comment.—Juvenile DM is now believed to have an autoimmune basis.[1] Thus, our patient displays evidence of three diseases of autoimmune origin: juvenile DM, Hashimoto's thyroiditis, and JRA. To our knowledge, she is the second reported patient with this combination of diseases; a previous case was presented as part of a clinicopathologic conference in 1968.[2] The diagnosis of JRA is supported in our patient by the clinical, radiologic, and laboratory findings. Histocompatibility antigen typing showed B27, but not B8. Other diseases of autoimmune origin were ruled out.

Clinical and serologic associations between juvenile DM and thyroid disorders, including Hashimoto's thyroiditis, have been established.[3] An

association between adult rheumatoid arthritis (but not JRA) and Hashimoto's thyroiditis is also known.[4] To date, there has been no established association between juvenile DM and JRA, although reports of juvenile DM concommitant with other connective tissue diseases have been noted.[5]

As Collen et al remarked in regard to their patient, we believe that our patient displays a widespread autoimmune disturbance of which the three diseases are individual manifestations. The eczema may be a fourth manifestation.[6] We believe that the association of JRA and the autoimmune endocrinopathies is not a fortuitous finding, and we expect that additional reports of such cases will be forthcoming.

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1. Maclaren NK: Viral and immunologic bases of beta cell failure in insulin-dependent diabetes. *Am J Dis Child* 131:1149-1154, 1977.

2. Castleman B (ed): Case records of the Massachusetts General Hospital, case 44-1968. *N Engl J Med* 279:987-996, 1968.

3. MacEvish AC, Irvine WJ: Autoimmunologic aspects of diabetes mellitus. *Clin Endocrinol Metab* 4:435-471, 1975.

4. Buchanan WW: The relationship of Hashimoto's thyroiditis to rheumatoid arthritis. *Geriatrics* 20:941-948, 1965.

5. Fruman LS: Diabetes mellitus, islet cell antibodies, and HLA-B8 in a patient with systemic lupus erythematosus. *Am J Dis Child* 131:1252-1254, 1977.

6. McGeady SJ, Buckley RH: Depression of cell-mediated immunity in atopic eczema. *J Allergy Clin Immunol* 56:393-406, 1975.

Hearing Loss and Learning Disability

Sir.—In a recent JOURNAL (132:1100-1104, 1978), Zinkus et al reported that children who have had a history of severe, chronic otitis media suffer later from developmental and learning problems. They conclude that hearing loss is the culprit.

Although they refer to an earlier article by Kaplan et al,[1] the authors fail to note that those investigators found no relationship between the degree of otitis media–caused hearing loss and learning problems. Kaplan et al found only the same correspondence between chronic otitis media and learning disorders that Zinkus found.

There is no evidence that the mild hearing loss associated with otitis media causes poor learning, nor is it known what causes the relationship between otitis media and learning disorder. I have suggested elsewhere[2] that a third factor, related to the predisposition to learning disability, may be responsible for the occurrence of chronic otitis media as well.

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1. Kaplan GJ, Fleshman JK, Bender TR, et al: Long-term effect of otitis media. *Pediatrics* 52:577-585, 1973.

2. Hersher L: Minimal brain dysfunction and otitis media. *Percept Mot Skills* 47:723-726, 1978.

In Reply.—To conceptualize the results of our investigations as a statement that otitis media-related hearing loss causes poor learning is oversimplistic and reflects a lack of understanding. We have suggested that transient hearing loss and distortion of auditory signals during the early language-formative years results in deficiencies in language development. One aspect of receptive language, auditory processing, may be compromised, with effects observed in academic areas. By disrupting the normal sequence of language development, the repeated episodes of otitis media-induced hearing loss have an indirect effect on subsequent academic performance.

A considerable body of evidence exists that confirms that hearing loss, associated with early chronic otitis media, compromises a child's language development.[1] The effects of hearing loss can be observed even during the prelinguistic babbling phases of early infancy.[2] Additionally, otitis media-induced hearing loss has been associated with deficiencies in receptive language, expressive language, and verbal intelligence.[3] There can be little doubt that the deficiencies in language development seen in young children with chronic otitis media result to a large degree from impaired auditory acuity.

We are further concerned with otitis media-produced hearing loss in infants and young children. It seems pretentious to assume that any hearing loss during this period of language development is "mild" in relation to the same degree of loss in adults. As Howie[4] has suggested, hearing loss in infancy and early childhood is more critical since the children have "little previous auditory experience." In this case, "mild" loss may not mean mild effect. Unfortunately, the fragile sequence of language development does not adhere to the arbitrary scaling of severity of hearing loss. Deprivation of high quality auditory input during the first two to three years of life may result from as little as 15 dB threshold.[1]

We have attempted to avoid nebulous and often ambiguous terms, such as learning disability or learning disorder. Instead, we have focused on those aspects of information processing that are most closely related to the auditory mechanism, ie, auditory processing. Our subjects with severe chronic otitis media consistently evidenced delays in their ability to use the full receptive capabilities of the auditory mechanism. Their ability to process auditory information was deficient, a fact that was evidenced in delayed language and, later, in disrupted auditory processing skills. Deficiencies in auditory processing are known to disrupt reading and spelling skills, as was found in our study.

We have offered this hypothesis as a beginning point for further testing, hopefully through future longitudinal prospective studies. In response to Herscher's statement, I would agree that other variables may predispose some children to be high risk candidates for more severe sequelae related to their otitis media. However, we did not imply that hearing loss associated with otitis media *causes* poor learning. Rather, there are language-related sequelae that reduce the ability of the child to process auditory information, and these effects may be seen even after the ear disease has been resolved.

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1. Downs MP: Hearing loss: Definition, epidemiology and prevention. *Pub Health Rev* 4:255-280, 1975.

2. Menyuk P: Effects of hearing loss on language acquisition in the babbling stage, in Jaffe B (ed): *Hearing Loss in Children*. Baltimore, University Park Press, 1977, pp 621-629.

3. Lewis N: Otitis media and linguistic incompetence. *Arch Otolaryngol* 102:387-390, 1976.

4. Howie VM: Acute and recurrent acute otitis media, in Jaffe B (ed): *Hearing Loss in Children*. Baltimore, University Park Press, 1977, pp 421-430.

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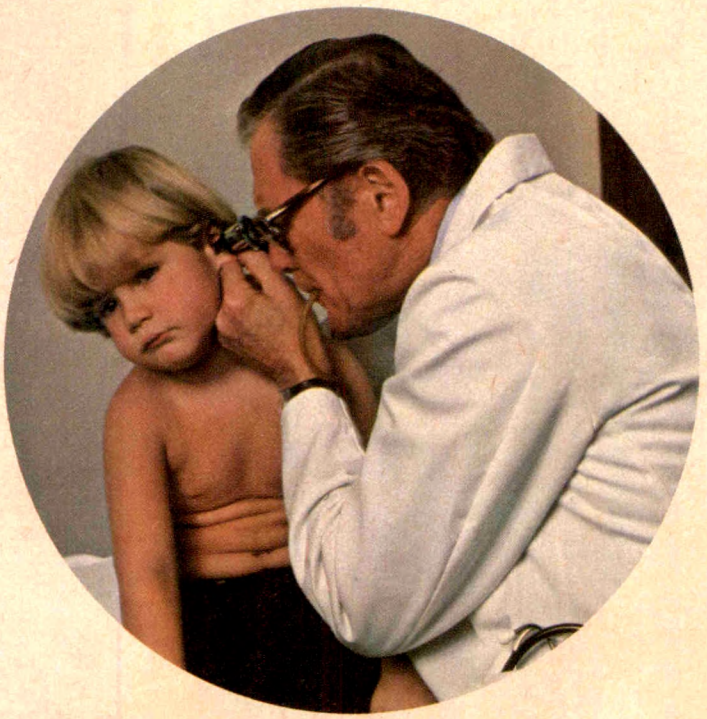
Ceclor®
cefaclor

A newly developed oral antibiotic useful in acute otitis media*



*Pneumococci, susceptible strains of Streptococcus pneumoniae (Diplococcus pneumoniae), *Haemophilus influenzae*, staphylococci,

A newly developed oral antibiotic

Ceclor® cefaclor

Consider the changing bacterial

Increasing incidence of otitis media caused by H. influenzae

Reports from many areas of the country show that the bacterial pattern seen in otitis media is changing. Published studies suggest that the incidence of otitis media caused by *H. influenzae* is increasing.[1,2]

In fact, the American Academy of Pediatrics' Committee on Infectious Diseases reports that relapses of otitis media have been more common with *H. influenzae* than with other organisms.[3]

H. influenzae resistance is a growing problem

Percentage of Ampicillin-Resistant *H. influenzae* Isolates*

	1975	1976	1977
Boston[4]	5.3%	10.2%	15.6%
Fresno[5]	—	—	4.8
Huntsville[4]	1.4	2.8	13.6
Washington, D.C.[6]	1.6	18	35
Oklahoma City[7]	—	—	22

*Isolates obtained from a variety of body fluids (middle-ear exudate, blood, etc.).

Recommendations regarding treatment of otitis media caused by H. influenzae

The American Academy of Pediatrics, in its recommendations for the treatment of otitis media, reports that *H. influenzae* is often the suspected pathogen in children less than eight years of age. They further report that ampicillin-resistant strains of *H. influenzae* have been isolated. The physician should therefore consider ampicillin resistance in the child with acute otitis media, particularly one who does not show clinical improvement after 48 to 72 hours of ampicillin therapy.[8]

Investigators have suggested a need for alternative antimicrobials in the treatment of otitis media caused by ampicillin-resistant *H. influenzae*.[9,10]

Ceclor® (cefaclor) is effective in the treatment of acute otitis media due to susceptible strains of these microorganisms:

- *S. pneumoniae*
- *H. influenzae* (including beta-lactamase-producing ampicillin-resistant strains)
- Staphylococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains)
- *S. pyogenes* (group A beta-hemolytic streptococci)

In studies of 246 patients with otitis media, Ceclor demonstrated a 93 percent clinical and bacteriologic success rate (see accompanying chart).[11]

Clinical and Bacteriologic Responses by Pathogen in 246 Infants and Children with Otitis Media[11]

		Satisfactory Responses	
Pathogen	Number of Patients	Clinical (Symptomatic)	Bacteriologic
S. pneumoniae	127	121	121
S. pyogenes	11	11	11
Staphylococcus aureus	21	18	19
H. influenzae	74	67	66
Multiple organisms	13	12	12
Totals	246	229 (93%)	229 (93%)

See the following page for criteria for diagnosis and response.

pattern of acute otitis media*

Good taste and t i d administration may aid patient compliance

Ceclor may be administered t i d. The pleasant-tasting oral suspensions encourage patient cooperation:

125 mg/5 ml, strawberry flavor
250 mg/5 ml, grape flavor

Criteria for diagnosis and response

Diagnosis:
Diagnosis of otitis media was confirmed in all patients by culture of middle-ear aspirate or exudate within 24 hours after the start of therapy. Exudate was acceptable as a culture source for only pneumococci, *H. influenzae*, and group A streptococci. Additional specimens for culture were obtained during and after therapy as deemed necessary by the clinician. The bacteriologic response was based on results during the ten to 16-day posttherapy follow-up period.

Clinical (symptomatic) response:
Satisfactory = disappearance of or improvement in signs and symptoms of the principal infection, with or without recurrence of signs or symptoms during the posttherapy follow-up period.

Unsatisfactory = no improvement in signs and symptoms at the end of therapy.

Bacteriologic response:
Cure = pathogen(s) eliminated or reduced to insignificant numbers during therapy or elimination of the original pathogen during therapy, followed by a culture positive for a new pathogen (reinfection) either during therapy or during the posttherapy follow-up period.

Failure = failure of the treatment to eradicate the pathogen(s) or initial eradication of the pathogen(s), followed by relapse with the same pathogen during therapy or during the posttherapy follow-up period.

Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

*Due to susceptible strains of *S. pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes*.

Ceclor® (cefaclor) is also indicated for these other common infections

Clinical trials have demonstrated the effectiveness of Ceclor against the following common infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections
including pneumonia caused by *S. pneumoniae*, *H. influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Upper respiratory infections
including pharyngitis and tonsillitis caused by *S. pyogenes* (group A beta-hemolytic streptococci)

Urinary tract infections
including pyelonephritis and cystitis caused by *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and coagulase-negative staphylococci

Skin and skin-structure infections
caused by *S. aureus* and *S. pyogenes* (group A beta-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See summary of prescribing information.

See the following page for summary of prescribing information.

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•A newly developed oral antibiotic

Ceclor® cefaclor

Pediatric Dosage			
Mild to Moderate Infections (20 mg/kg/day)			
125 mg (½ tsp t i d)		**125 mg** (1 tsp t i d)	**250 mg** (1 tsp t i d)
0-20 lb 0-9 kg		20-40 lb 9-18 kg	40-55 lb 18-25 kg
More Serious Infections and Otitis Media* (40 mg/kg/day)			
125 mg (½ tsp t i d)	**125 mg** (1 tsp t i d)	**250 mg** (1 tsp t i d)	**250 mg** (1 gm in 3 divided doses)
0-10 lb 0-4.5 kg	10-20 lb 4.5-9 kg	20-40 lb 9-18 kg	40-55 lb 18-25 kg

125 mg, Strawberry 250 mg, Grape

The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every eight hours.

In more serious infections, otitis media,* and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 gm per day.

Safety for use in infants less than one month of age has not been established.

*Due to susceptible strains of *S. pneumoniae, H. influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).

References

1. Pediatr. Clin. North Am., *21*:379, 1974.
2. J.A.M.A., *238*:1032, 1977.
3. Report of the Committee on Infectious Diseases, p. 109. Evanston, Illinois: American Academy of Pediatrics, 1977.
4. J. Pediatr., *92*:889, 1978.
5. West. J. Med., *128*:101, 1978.
6. J.A.M.A., *239*:320, 1978.
7. Med. Trib., *18*:1 (November 16), 1977.
8. Report of the Committee on Infectious Diseases, p. 162. Evanston, Illinois: American Academy of Pediatrics, 1977.
9. Curr. Chemother., *1*:123, 1978.
10. Am. J. Dis. Child., *132*:992, 1978.
11. Data on file, Eli Lilly and Company.

Ceclor® (cefaclor)

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci)

Lower respiratory infections, including pneumonia caused by *S. pneumoniae (D. pneumoniae), H. influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Upper respiratory infections, including pharyngitis and tonsillitis caused by *S. pyogenes* (group A beta-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections, including pyelonephritis and cystitis caused by *Escherichia coli, Proteus mirabilis, Klebsiella* species, and coagulase-negative staphylococci

Skin and skin-structure infections caused by *Staphylococcus aureus* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor® (cefaclor, Lilly), should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below:

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

Administration and Dosage:

Ceclor® (cefaclor, Lilly) is administered orally.

Adults—The usual adult dosage is 250 mg every eight hours. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled. Doses of 4 gm per day have been administered safely to normal subjects for 28 days, but the total daily dosage should not exceed this amount.

Children—The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every eight hours, as indicated:

Child's Weight	Ceclor Suspension 125 mg/5 ml	Ceclor Suspension 250 mg/5 ml
9 kg	1/2 tsp t i d	
18 kg	1 tsp t i d	1/2 tsp t i d

In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 gm per day.

Ceclor may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see Precautions).

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of Ceclor should be administered for at least ten days. [070379]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46206.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

Lilly

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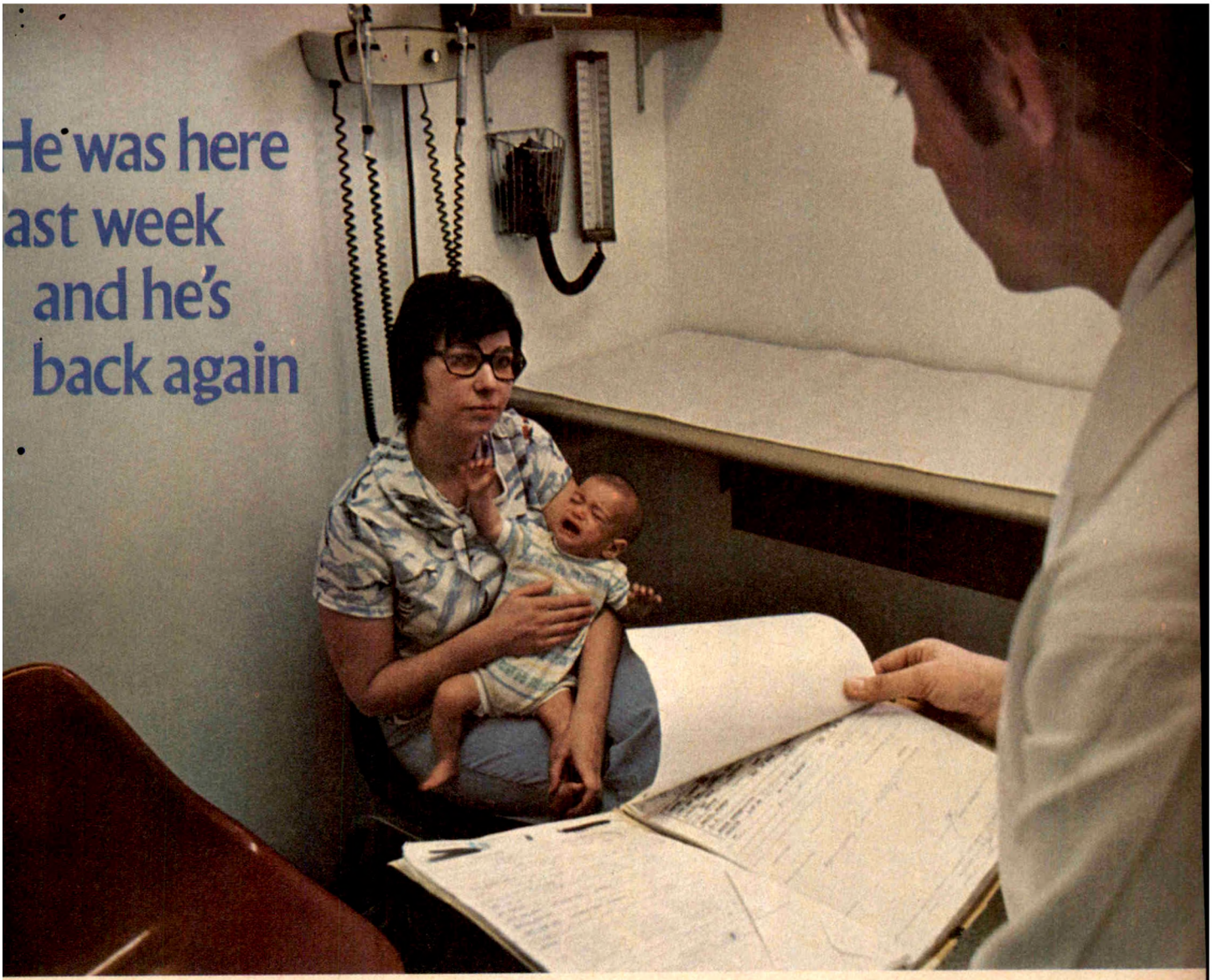

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The physical symptoms are many and varied: diarrhea, colic, eczema, asthma, vomiting, bronchitis, rhinitis. They can be coupled with behavioral symptoms: repeated refusal of the nursing bottle . . . general fussiness.[1-3]

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With Isomil® Soy Protein Formula you can avoid the symptoms of milk sensitivity and help confirm your initial diagnosis.

Moreover, Isomil promotes normal growth.[2,5] It looks like milk, it pours like milk and has a pleasant aroma, which help insure acceptability. Unlike milk, Isomil is lactose free. It avoids the possibility of prolonged or recurring diarrhea caused by lactose intolerance.

Consider the possibility of milk sensitivity when associated symptoms are presented. "A high index of suspicion" is essential to its prompt detection.[2,6]

References: 1. Rapp, D. J.: Milk Allergy — From Birth to Old Age. Consultant 14:120, 1974. 2. Cowan, C.C., Brownlee, R.C., DeLoache, W.R., Jackson, H.P., and Matthews, J.P.: A Soy Protein Isolate Formula in the Management of Allergy in Infants and Children. South. Med. J. 62:389, 1969. 3. Clein, N.W.: Cow's Milk Allergy in Infants and Children. Int. Arch. Allergy. 13:245, 1958. 4. Goldman, A.S., Anderson, D.W., Sellars, W.A., Saperstein, S., Kniker, W.T., Halpern, S.R.: Milk Allergy. 1. Oral Challenge with Milk and Isolated Milk Proteins in Allergic Children. Ped. 32:425, 1963. 5. Jung AL, Carr SL: A soy protein formula and a milk-based formula. Clin.Ped. 16:982, 1977. 6. Frier, S. and Kletter, B.: Milk Allergy in Infants and Young Children. Clin. Ped. 9:449, 1970.

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In pediatric infections

Septra®

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

Suspension B.I.D.

Acute
Otitis
Media

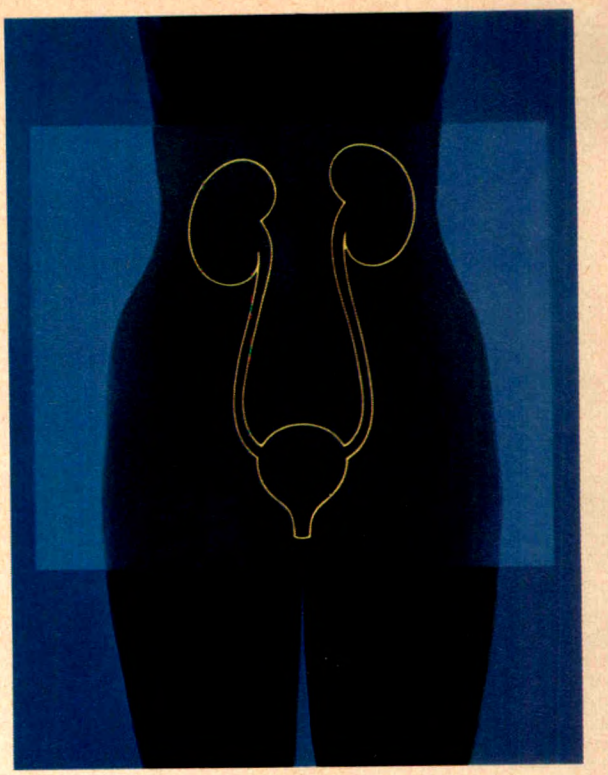
where the action is.

In acute otitis media

- Septra Suspension provides effective antibacterial action against susceptible strains of H influenzae and S pneumoniae (D pneumoniae), the pathogens most likely to cause acute otitis media in children.

Septra Suspension is useful in many patients, but especially in those with penicillin allergy or with infections caused by ampicillin-resistant H influenzae. Limited clinical data are presently available on the effectiveness of treatment of acute otitis media with Septra when the infection is due to H influenzae resistant to ampicillin. However, in vitro data is highly favorable; when over 200 strains of ampicillin-resistant H influenzae were tested, all proved susceptible to TMP/SMX.*

And unlike most other antibacterials for the treatment of acute otitis media, Septra Suspension is administered on a convenient b.i.d. dosage schedule. The cherry-flavored suspension is well accepted by children.



In recurrent urinary tract infections

Septra Suspension provides effective antibacterial action in urine and blood against susceptible strains of E coli, Klebsiella-Enterobacter and Proteus. Whether the infection centers in the kidneys or bladder, Septra Suspension maintains effective levels at the site of the infection with just two doses a day.

Adequate fluid intake should be maintained and frequent urinalyses with careful microscopic examination performed during Septra therapy. Septra is contraindicated in infants under two months of age.

*In vitro data do not necessarily correlate with clinical results. Data on file, Burroughs Wellcome Co.
NOTE: Septra should not be used in the treatment of streptococcal pharyngitis.

Please see prescribing information on next page.

ONE HUNDRED YEARS WELLCOME
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Septra® Suspension B.I.D.

Each teaspoonful (5 ml) contains: 40 mg trimethoprim and 200 mg sulfamethoxazole

Septra® DS B.I.D.

Each tablet contains: 160 mg trimethoprim and 800 mg sulfamethoxazole

Septra® DS Tablets Double Strength
Septra® Tablets
Septra® Suspension

INDICATIONS AND USAGE:
URINARY TRACT INFECTIONS: **For the treatment of urinary tract infections due to susceptible strains of the following organisms:** *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.**

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: **For the treatment of acute otitis media in children due to susceptible strains of** *Haemophilus influenzae* **or** *Streptococcus pneumoniae* **when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to** *Haemophilus influenzae* **resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.**

SHIGELLOSIS: **For the treatment of enteritis caused by susceptible strains of** *Shigella flexneri* **and** *Shigella sonnei* **when antibacterial therapy is indicated.**

PNEUMOCYSTIS CARINII **PNEUMONITIS: For the treatment of documented** *Pneumocystis carinii* **pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.**

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septra may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septra is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose —every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	½
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1½
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

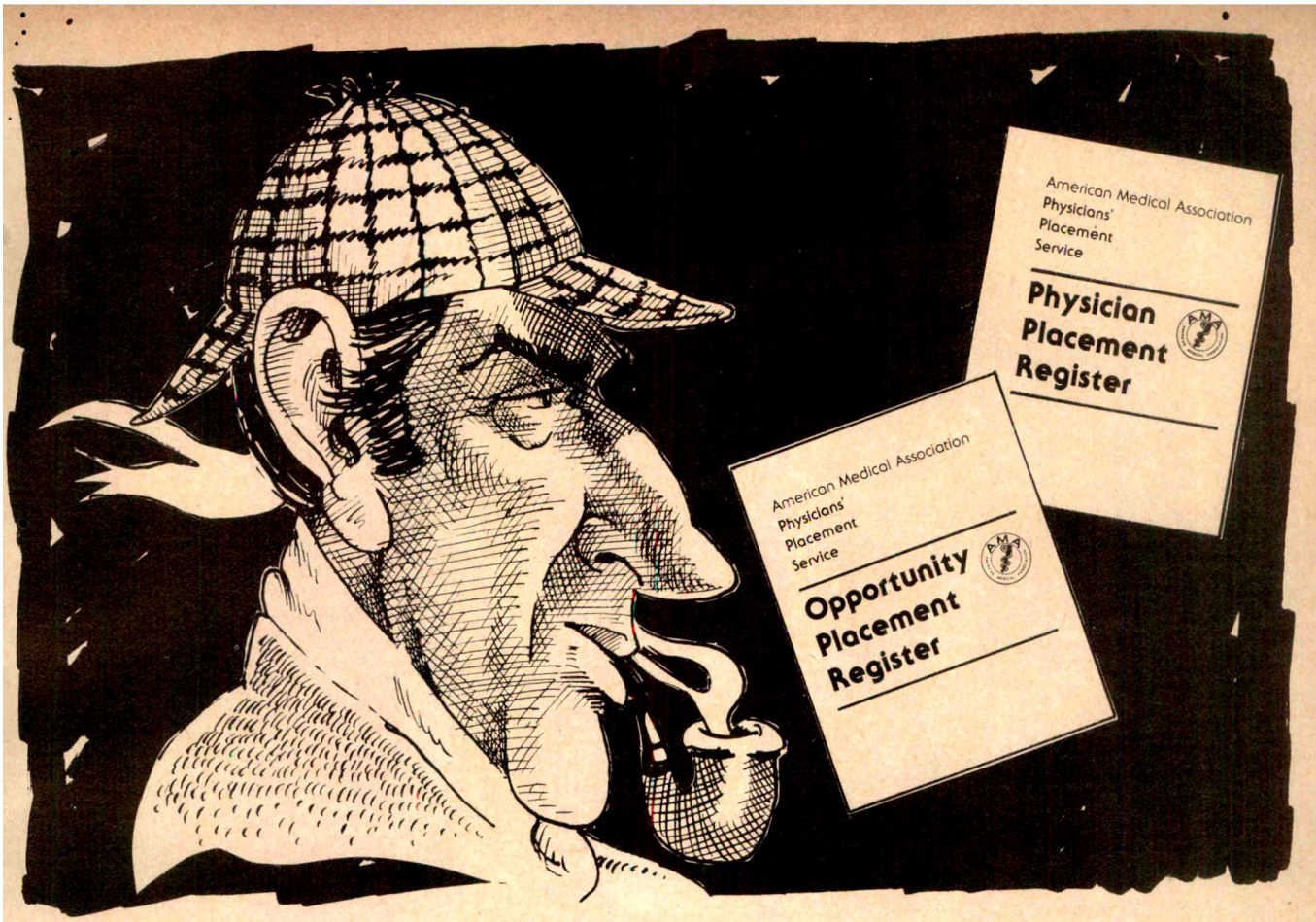
PNEUMOCYSTIS CARINII **PNEUMONITIS:**
The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose —every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	½
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1½
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

ONE HUNDRED YEARS WELLCOME
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709



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SYNEMOL®
(FLUOCINOLONE ACETONIDE)
CREAM 0.025%

Description SYNEMOL (fluocinolone acetonide) has the chemical name 6α, 9α-difluoro-16α-hydroxyprednisolone-16, 17-acetonide.

The cream contains fluocinolone acetonide 0.25 mg./g. in a water-washable aqueous emollient base of stearyl alcohol, cetyl alcohol, mineral oil, propylene glycol, sorbitan monostearate, polysorbate 60, purified water and citric acid.

Indications Inflammatory manifestations of corticosteroid-responsive dermatoses.

Contraindications Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Precautions If irritation develops, discontinue the product and institute appropriate therapy.

In the presence of an infection institute the use of an appropriate antifungal or antibacterial agent. If a favorable response does not occur promptly, discontinue the corticosteroid until the infection has been adequately controlled.

If extensive areas are treated or if occlusive technique is used, there will be increased systemic absorption of the corticosteroid and suitable precautions should be taken, particularly in children and infants.

The safety of topical steroids in pregnant women has not absolutely been established. In laboratory animals, increases in incidences of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids, in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts or for prolonged periods of time.

SYNEMOL® (fluocinolone acetonide) cream is not for ophthalmic use.

Adverse Reactions Local adverse reactions reported with topical corticosteroids: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

How Supplied
SYNEMOL® (fluocinolone acetonide) Cream 0.025%—15, 30 and 60 g. tubes.

SYNTEX

Syntex Laboratories, Inc.
Palo Alto, California 94304

A PROVEN TOPICAL STEROID

EFFECTIVE NEARLY EVERYWHERE† FOR NEARLY EVERYONE.

*For the inflammatory manifestations of steroid-responsive dermatoses

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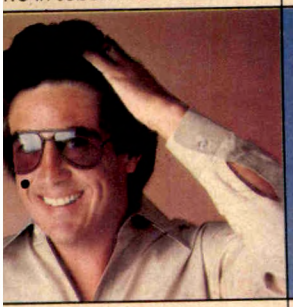			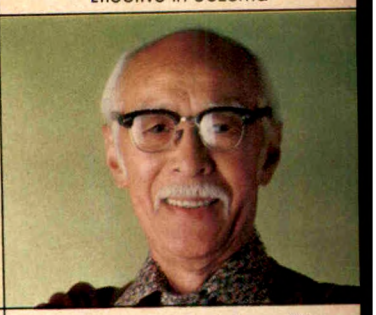
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			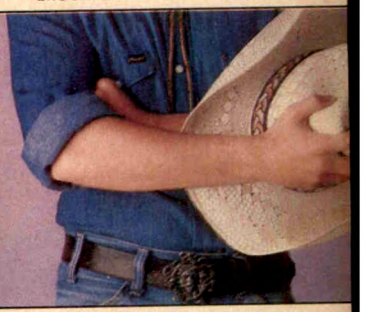
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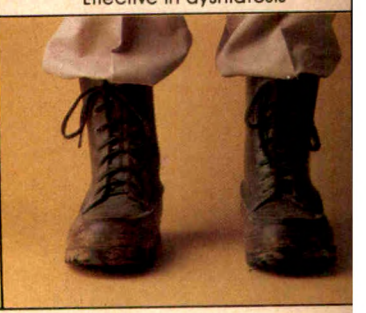
ffective in neurodermatitis*	Effective in xerotic eczema*	Effective in poison ivy*	Effective in dyshidrosis*
			

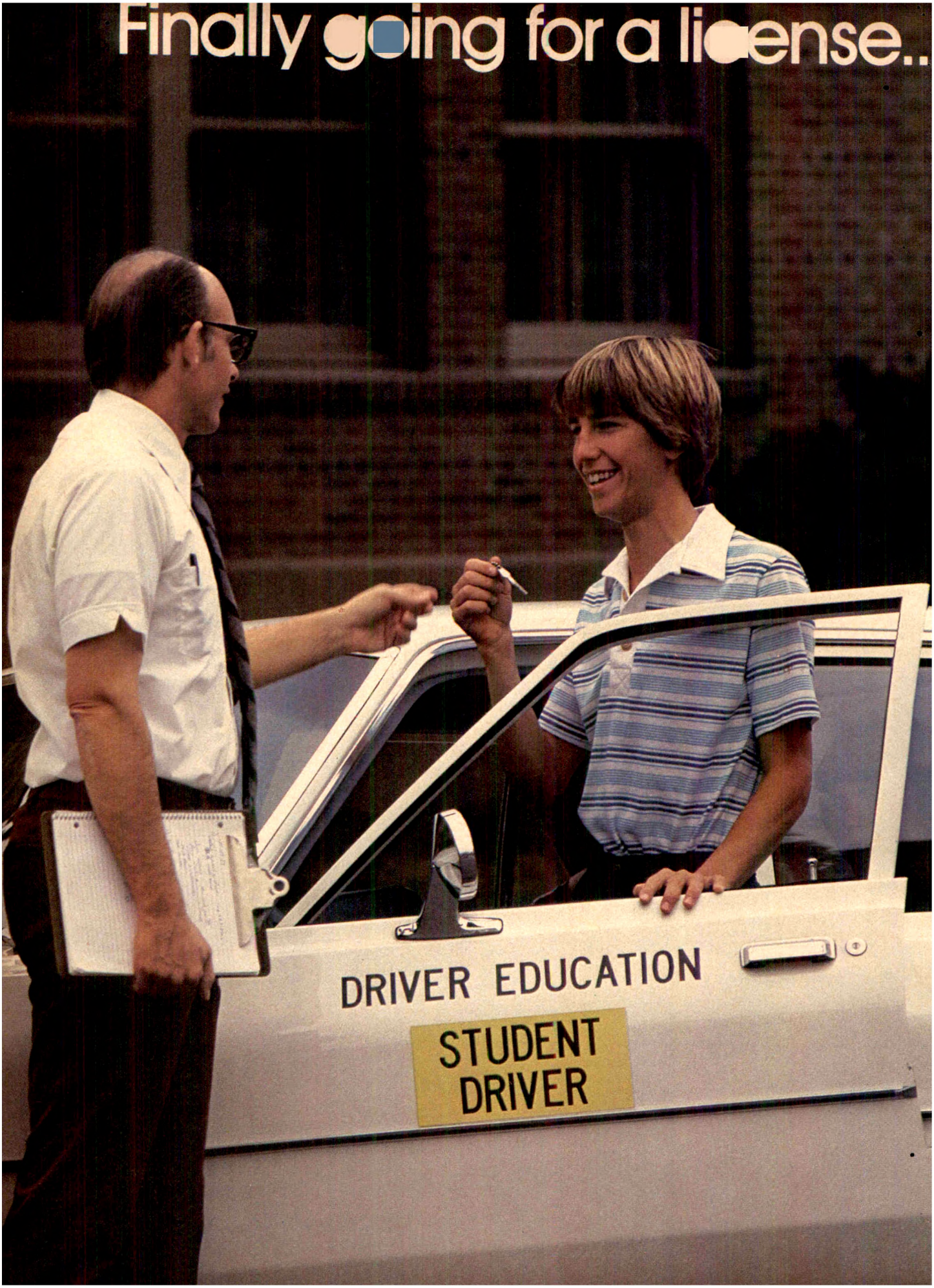
CREAM 0.025%

SYNEMOL®

(FLUOCINOLONE ACETONIDE)

ONE FORM. ONE STRENGTH. ONE PRESCRIPTION.

† Not for ophthalmic use. Please see preceding page for summary of prescribing information.


Finally going for a license..
DRIVER EDUCATION
STUDENT
DRIVER

inally going for a license...

a better life with Depakene®
Valproic Acid

or your patients with mixed seizures ncluding absence, or pure absence

lore than just effective eizure control[1]

28 studies of patients with mixed grand mal and sence, 76% of all patients gained significant provement; over one-third became seizure-free. 60 studies involving pure absence, 86% of atients were improved; half became seizure-free.

eedom from social stigmata important too

ith Depakene, social function is unimpeded by ug-induced hirsutism or gingival hyperplasia. tellectual function may improve as more edative drugs are reduced in dosage or ithdrawn. Patients may be able to lead a more ormal life with Depakene than was possible with eir previous drug regimen.

widely useful anticonvulsant

epakene is indicated as sole or adjunctive erapy in both simple and complex absence eizures. It is also indicated for adjunctive eatment of patients with multiple seizure types hich include absence. Clinical response has een especially noteworthy among patients with eneralized tonic-clonic attacks, or with minor otor seizures (e.g., myoclonic movements, kinetic seizures), where combined with absence.

Offering your patients a chance for a better life

Sustained freedom from seizures can mean a drivers license, an active social schedule, involvement in athletic competition—a better life for your patient. Depakene has not been associated with hirsutism or gingival hyperplasia. Sedation has not been a frequent problem. The most common side effect with Depakene is G.I. upset, which usually responds to temporary dosage reduction. Serious side effects, including fatal hepatitis, have occurred.

1. Worldwide studies of Depakene experience (Data refer only to grand mal and/or absence seizures. Since each type was evaluated separately, some patients appear in both groups. Though most of these studies were uncontrolled and had widely differing protocols, their collective data clearly support efficacy of the drug).

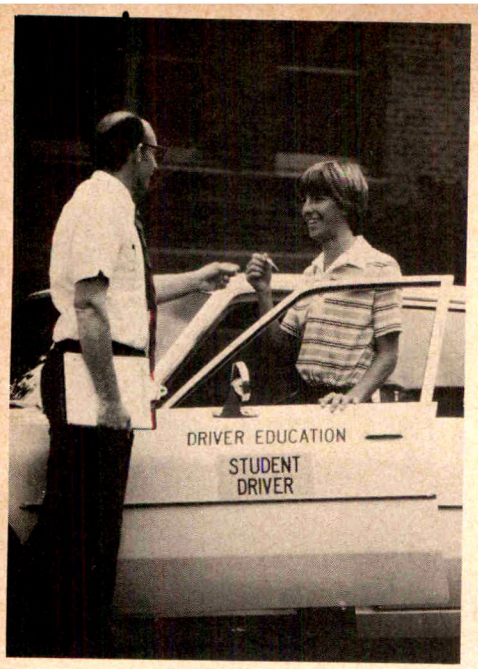
See overleaf for brief summary of prescribing information

Abbott Laboratories,
North Chicago, Illinois 60064

0013326R

Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

Depakene®
Valproic Acid



Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

A BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremo dysarthria, dizziness, and incoordination have rarely been note Rare cases of coma have been noted in patients also on phenoba bital.

Dermatologic: Transient increases in hair loss have been ol served. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggressio hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproi acid inhibits the secondary phase of platelet aggregation. (Se DRUG INTERACTIONS). This may be reflected in altered bleedin time. Bruising, hematoma formation and frank hemorrhage hav been reported. Relative lymphocytosis and hypofibrinogenemi have been noted. Leukopenia and eosinophilia have also been re ported.

Hepatic: Increases in serum alkaline phosphatase and elevation of serum glutamic oxaloacetic transaminase (SGOT) have bee noted. Elevation of SGOT may be dose related. Elevations of SGP and LDH have been noted less frequently. Isolated cases of sever hepatotoxicity have been reported but do not appear dose related (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic aci has been reported. After ingesting 36 grams in combination wit phenobarbital and phenytoin, the patient presented in deep coma An electroencephalogram recorded diffuse slowing, compatibl with the state of consciousness. The patient made an uneventfu recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increased dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

0013326

ABBOTT

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Head's all clear, too!

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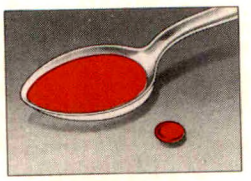

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Recommend Sudafed... For decongestion without drowsiness

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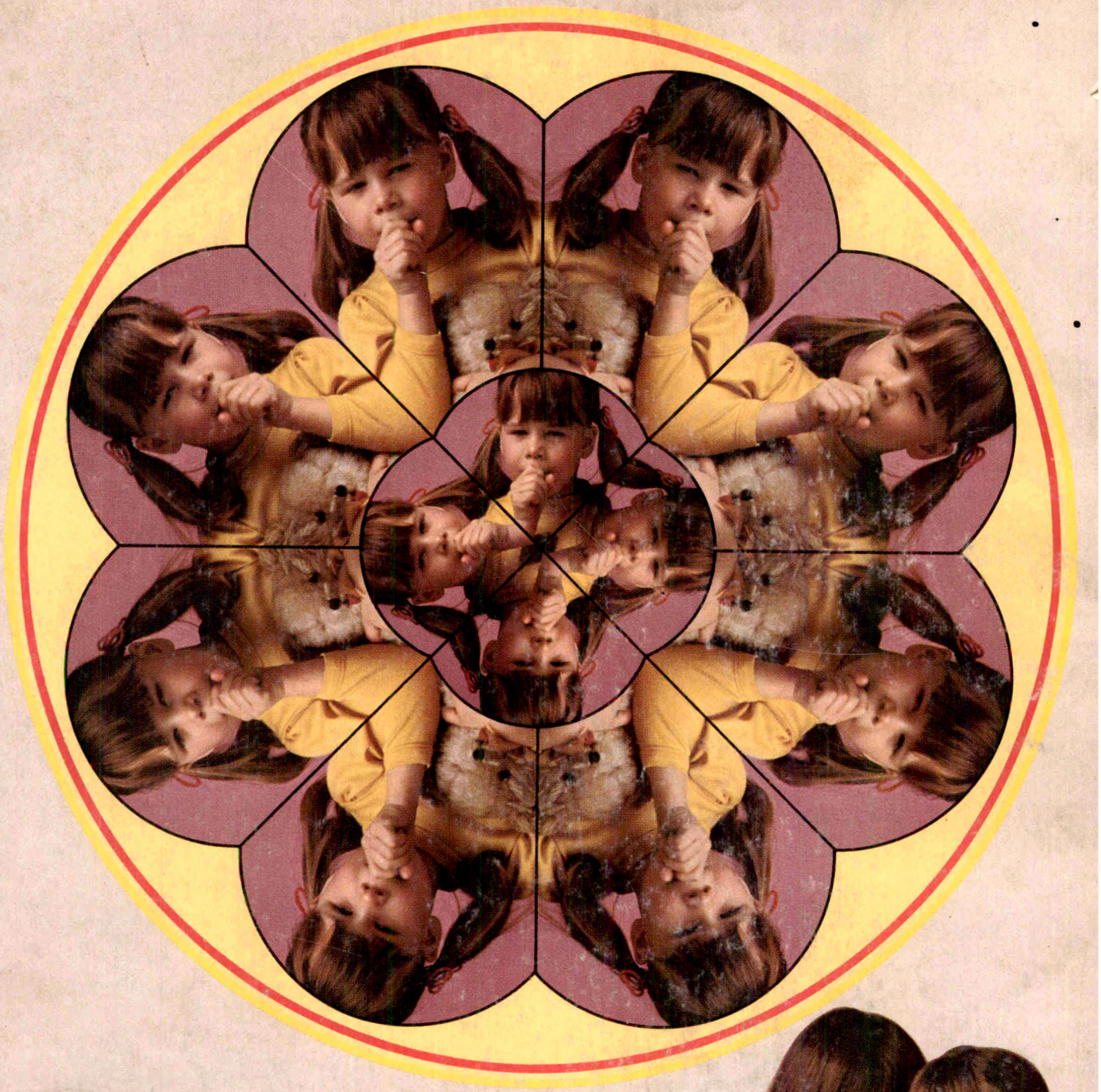

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Lacking in substantial evidence of effectiveness as a fixed combination: For relief from coughing, upper respiratory congestion and hypersecretion associated with the common cold, sinusitis, vasomotor rhinitis and allergic rhinitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any component; concurrent MAO inhibitor therapy; severe hypertension; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Do not use 'Tuss-Ornade' Liquid in children less than six months of age or under 15 lbs. in weight. Do not use 'Tuss-Ornade' *Spansule* capsules in children under 12 years of age.

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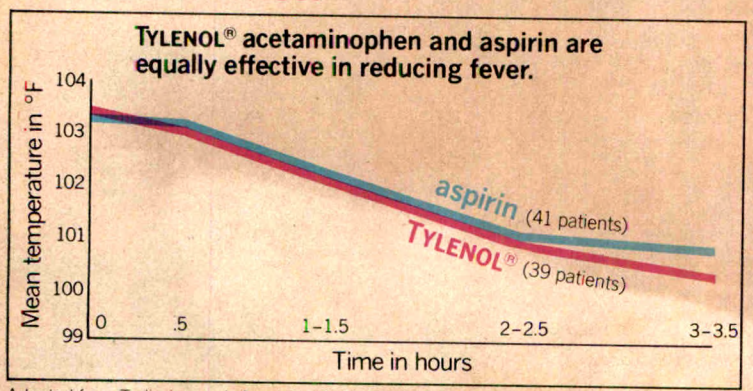

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Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Lacking substantial evidence of effectiveness as a fixed combination": For the symptomatic relief of cough in conditions such as: the common cold, acute bronchitis, allergic asthma, bronchiolitis, croup, emphysema, tracheobronchitis.

Final classification of the less-than-effective indications requires further investigation.

Warning: Use in Pregnancy: Experience with this drug in pregnant women is inadequate to determine whether there exists a potential for harm to the developing fetus.

Precautions: Although pseudoephedrine hydrochloride causes virtually no pressor effect in normotensive patients, it should be used with caution in patients with hypertension. In addition, even though triprolidine hydrochloride produces only a low incidence of drowsiness, appropriate precautions should be observed.

Side Effects: The great majority of patients will not have any side effects. Only certain patients, sensitive to one or another of the ingredients, may note mild stimulation or mild sedation.

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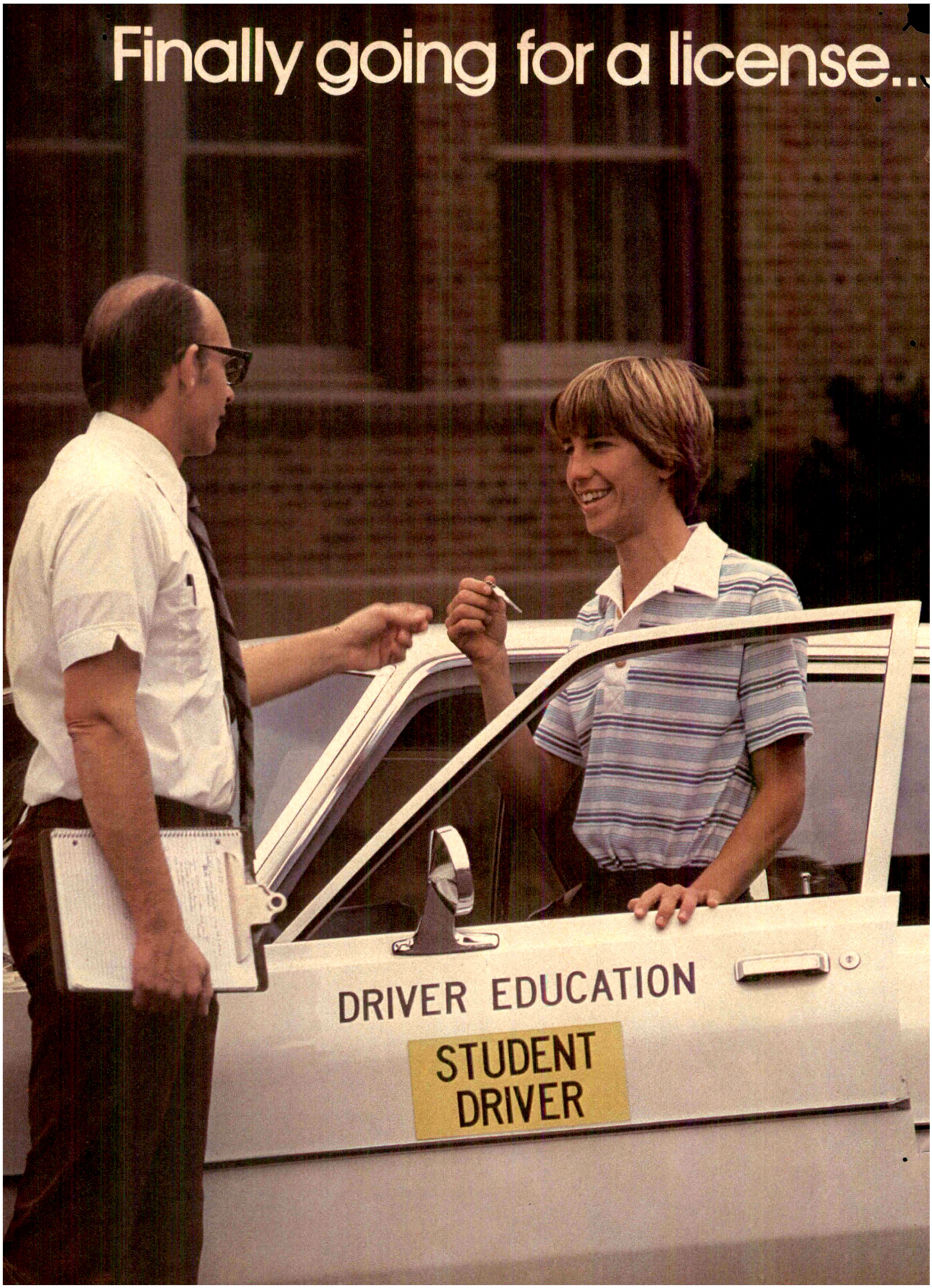
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See overleaf for brief summary of prescribing information

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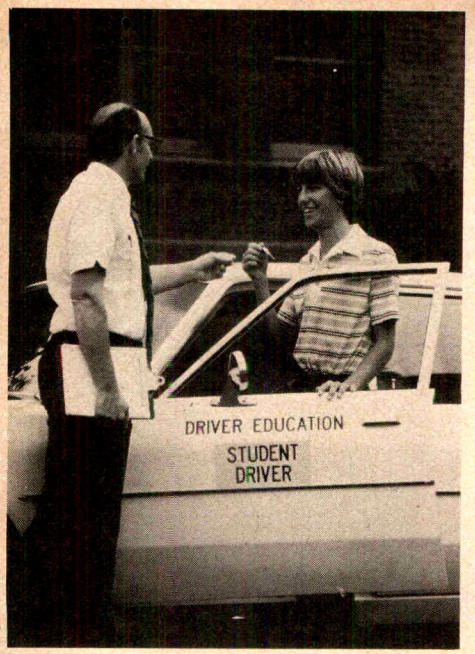

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A BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported but do not appear dose related. (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increased dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

0013326

ABBOTT

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General Information.—Send manuscripts by first-class (not registered) mail to the Chief Editor, Gilbert B. Forbes, MD, Box 777, 601 Elmwood Ave, Rochester, NY 14642. Designate one author as correspondent and provide his/her address and telephone number. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. Accepted manuscripts become the permanent property of the *American Journal of Diseases of Children* and may not be published elsewhere without permission from the publisher (AMA).

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Manuscript Preparation

All the elements of a manuscript should be submitted in **triplicate, double-spaced throughout.** Use heavy-duty white bond paper, 22 × 28-cm, and 4-cm margins. The style of writing should conform to proper English usage and syntax. All measurements are to be in metric units, temperatures in Centigrade.

All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Titles.—Titles should be short, specific, and clear. They should not exceed 42 characters per line, including punctuation and spaces, and be limited to two lines. The title page should include the full names and academic affiliations of all authors, the address to which requests for reprints should be sent, and, if the manuscript was presented at a meeting, the name of the organization, place, and date on which it was read.

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Informed Consent.—Manuscripts reporting the results of experimental investigations on humans must include a statement to the effect that informed consent was obtained from the parents or guardians after the nature of the procedure(s) had been fully explained.

Clinical Memoranda

Brief accounts of interesting observations and clinical situations. Limited to 800 words plus one table or illustration; abstract unnecessary. Submit in triplicate, double-spaced. Copyright assignment required.

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References

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1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 131:295-296, 1977.
2. Koller LR: *Ultraviolet Radiation*, ed 2. New York, John Wiley & Sons Inc, 1965, pp 141-160.
3. Daughaday WH: The adenohypophysis, in Williams RH (ed): *Textbook of Endocrinology*, ed 5. Philadelphia, WB Saunders Co, 1974, pp 31-79.

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Illustrations

Submit in triplicate, unmounted, and untrimmed. Send only high contrast glossy prints (not photocopies or original artwork); preferred size 12.5 × 18-cm. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed label and affixed to the back of each illustration. Lettering must be legible after reduction to column size. Magnification and stain should be provided for histologic sections.

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Acknowledgments.—Illustrations and tables from other publications must be suitably acknowledged, and accompanied by written permission from publisher and author.

Photographic Consents.—A signed statement of consent from **both** parents (or guardian) or the persons involved must accompany all photographs of patients in which a possibility of identification exists. It is not sufficient to cover the eyes to mask identity.

Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 22 × 28-cm paper. If a table must be continued, use a second sheet and repeat all heads. Each table must have a title

In pediatric infections

Septra®

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

Suspension B.I.D.

Acute
Otitis
Media

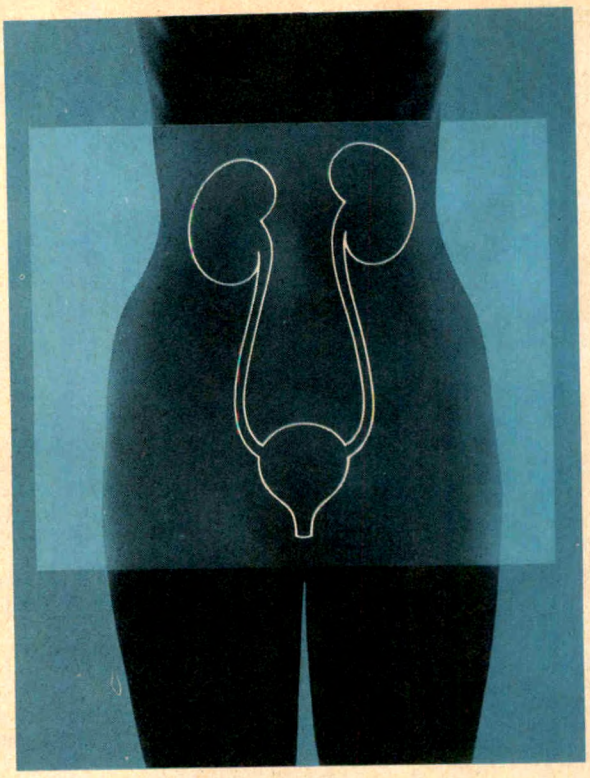
where the action is.

In acute otitis media

Septra Suspension provides effective antibacterial action against susceptible strains of H influenzae and S pneumoniae (D pneumoniae), the pathogens most likely to cause acute otitis media in children.

Septra Suspension is useful in many patients, but especially in those with penicillin allergy or with infections caused by ampicillin-resistant H influenzae. Limited clinical data are presently available on the effectiveness of treatment of acute otitis media with Septra when the infection is due to H influenzae resistant to ampicillin. However, in vitro data is highly favorable; when over 200 strains of ampicillin-resistant H influenzae were tested, all proved susceptible to TMP/SMX.*

And unlike most other antibacterials for the treatment of acute otitis media, Septra Suspension is administered on a convenient b.i.d. dosage schedule. The cherry-flavored suspension is well accepted by children.



In recurrent urinary tract infections

Septra Suspension provides effective antibacterial action in urine and blood against susceptible strains of E coli, Klebsiella-Enterobacter and Proteus. Whether the infection centers in the kidneys or bladder, Septra Suspension maintains effective levels at the site of the infection with just two doses a day.

Adequate fluid intake should be maintained and frequent urinalyses with careful microscopic examination performed during Septra therapy. Septra is contraindicated in infants under two months of age.

*In vitro data do not necessarily correlate with clinical results. Data on file, Burroughs Wellcome Co.
NOTE: Septra should not be used in the treatment of streptococcal pharyngitis.

Please see prescribing information on next page.

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Septra® Suspension B.I.D.

Each teaspoonful (5 ml) contains: 40 mg trimethoprim and 200 mg sulfamethoxazole

Septra® DS B.I.D.

Each tablet contains: 160 mg trimethoprim and 800 mg sulfamethoxazole

Septra® DS Tablets Double Strength
Septra® Tablets
Septra® Suspension

INDICATIONS AND USAGE:
URINARY TRACT INFECTIONS: **For the treatment of urinary tract infections due to susceptible strains of the following organisms:** *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.**

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: **For the treatment of acute otitis media in children due to susceptible strains of** *Haemophilus influenzae* **or** *Streptococcus pneumoniae* **when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to** *Haemophilus influenzae* **resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.**

SHIGELLOSIS: **For the treatment of enteritis caused by susceptible strains of** *Shigella flexneri* **and** *Shigella sonnei* **when antibacterial therapy is indicated.**

PNEUMOCYSTIS CARINII **PNEUMONITIS: For the treatment of documented** *Pneumocystis carinii* **pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.**

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septra may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septra is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose —every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	½
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1½
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII **PNEUMONITIS:**
The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose —every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	½
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1½
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

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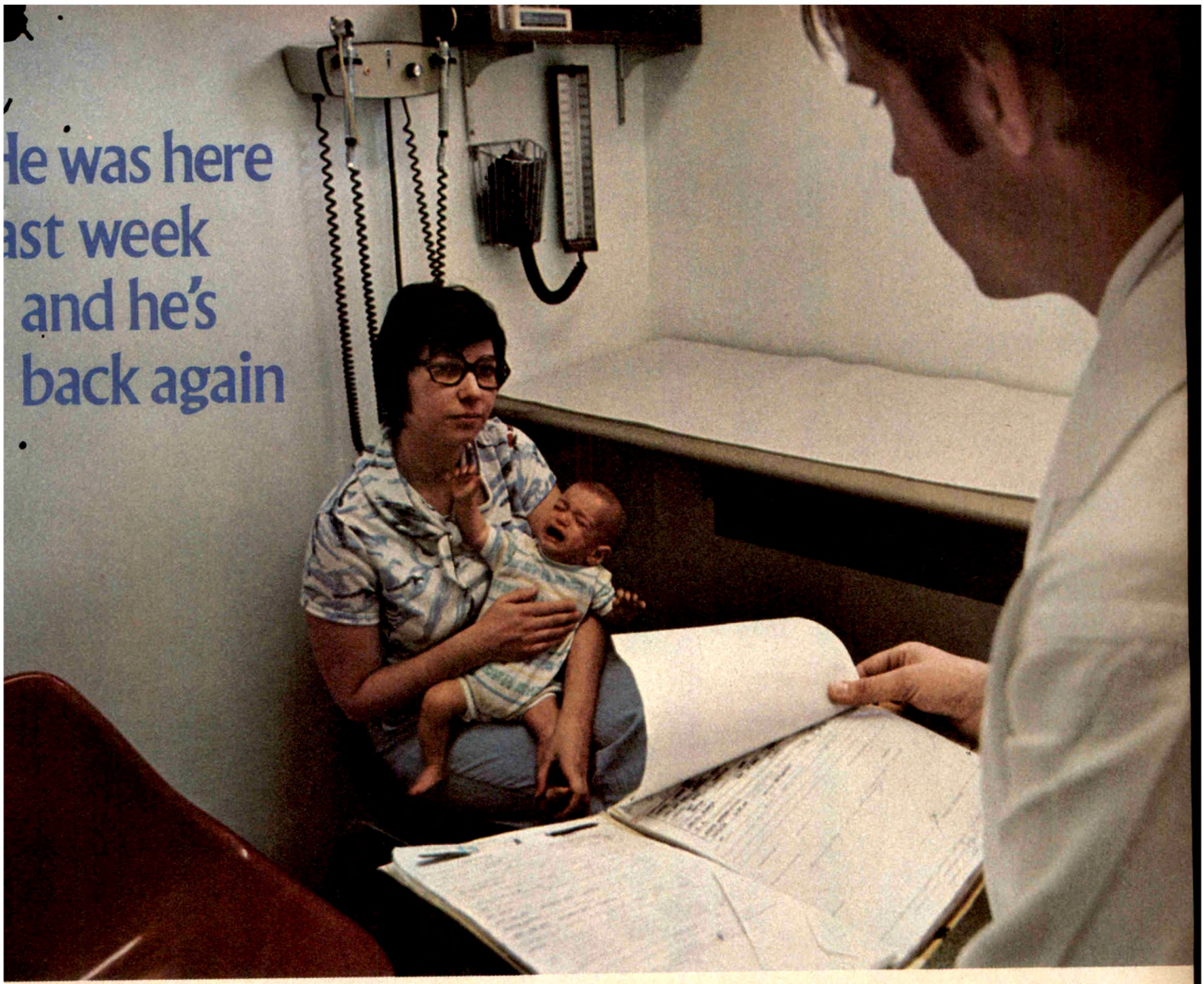

Have you ruled out cow-milk sensitivity?

The physical symptoms are many and varied: diarrhea, colic, eczema, asthma, vomiting, bronchitis, rhinitis. They can be coupled with behavioral symptoms: repeated refusal of the nursing bottle . . . general fussiness.[1-3]

Alone or together, the manifestations of milk sensitivity are an unnecessary burden for the infant . . . and parents. More important, if unchecked the allergic syndromes can lead to failure to thrive and other serious health problems.[4]

With Isomil® Soy Protein Formula you can avoid the symptoms of milk sensitivity and help confirm your initial diagnosis.

Moreover, Isomil promotes normal growth.[2,5] It looks like milk, it pours like milk and has a pleasant aroma, which help insure acceptability. Unlike milk, Isomil is lactose free. It avoids the possibility of prolonged or recurring diarrhea caused by lactose intolerance.

Consider the possibility of milk sensitivity when associated symptoms are presented. "A high index of suspicion" is essential to its prompt detection.[2,6]

References: 1. Rapp, D. J.: Milk Allergy — From Birth to Old Age. Consultant 14:120, 1974. 2. Cowan, C.C., Brownlee, R.C., DeLoache, W.R., Jackson, H.P., and Matthews, J.P.: A Soy Protein Isolate Formula in the Management of Allergy in Infants and Children. South. Med. J. 62:389, 1969. 3. Clein, N.W.: Cow's Milk Allergy in Infants and Children. Int. Arch. Allergy. 13:245, 1958. 4. Goldman, A.S., Anderson, D.W., Sellars, W.A., Saperstein, S., Kniker, W.T., Halpern, S.R.: Milk Allergy. 1. Oral Challenge with Milk and Isolated Milk Proteins in Allergic Children. Ped. 32:425, 1963. 5. Jung AL, Carr SL: A soy protein formula and a milk-based formula. Clin.Ped. 16:982, 1977. 6. Frier, S. and Kletter, B.: Milk Allergy in Infants and Young Children. Clin. Ped. 9:449, 1970.

Switch first to

ISOMIL®

Soy Protein Formula

when the baby can't take milk

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Get them on their feet again!

When winter colds are at their worst, Naldecon® is at its best!

(antihistamine/decongestant)

Winter colds can get even the best of sports down. But Naldecon® (antihistamine/decongestant) can get them up and going again with fast symptomatic relief!

With balanced formulation for maximum relief and minimum side effects.

Naldecon combines antihistamines from two chemical classes, as well as two decongestants, to offer prompt symptomatic relief and minimize side effects. That's why it's the ideal choice for busy, active patients who aren't going to let a cold stop them.

An ethanolamine for long-lasting antihistamine activity

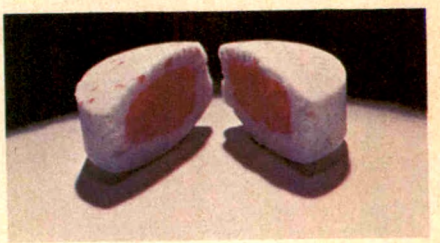
An alkylamine for minimal antihistamine drowsiness

Phenylpropanolamine for prolonged decongestant effectiveness

Phenylephrine for additional decongestant action with little or no C.N.S. stimulation.

With a unique tablet designed for easy titrating and hours of sustained relief.

With Naldecon tablets, adjusting dosage without losing the convenience of sustained relief is a snap! The unique Naldecon tablet is scored so that just a little thumb pressure on each half of the tablet breaks it neatly in two. Half tablet or whole, the outer layer rapidly dissolves for prompt effectiveness and the slow-release inner core provides additional hours of relief.



With enough dosage forms to keep the entire family skiing.

Naldecon's full line of forms for all ages includes "kid-tested and flavor-approved" pediatric liquids.

- Adult tablets and syrup.
- Pediatric syrup for infants and children, 6 months to 12 years old.
- Pediatric drops for infants and children, 3 months to 6 years old.

Naldecon® salutes the world's best.

XIII OLYMPIC WINTER GAMES LAKE PLACID 1980

The world's best winter athletes gather in Lake Placid this year for the quadrennial spectacle of the Olympic Winter Games. Bristol Laboratories takes great pride in having Naldecon designated Official Supplier to these XIII Olympic Winter Games.
We salute the splendid amateur athletes whose memorable feats are once again an inspiration to all of us who have trouble staying on our feet in the winter.

Naldecon®

(antihistamine/decongestant)

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Naldecon®
(antihistamine/decongestant)

Official Supplier to the XIII Olympic Winter Games in Lake Placid, New York.

XIII OLYMPIC WINTER GAMES LAKE PLACID 1980

Only Naldecon® offers the winter cold sufferer the effectiveness of *two* antihistamines and *two* decongestants, proportioned to minimize their undesirable side effects.

Naldecon® has:

- **Staying power.** Sustained release: an outer layer fo immediate relief, an inner core for hours more.
- **Flexibility.** Dosage forms for all ages and a unique scored tablet for fractionalized dosage, without losing the sustained release.
- **Balance.** Formulated to provide maximum effectiveness with minimum side effects.

NALDECON® Tablets, Syrup, Pediatric Drops, and Pediatric Syrup For Oral Use Only

5600DIMO-11 1/78

DESCRIPTION:

Each sustained-action tablet contains:	For immediate action	For delayed action	Total content
Phenylpropanolamine hydrochloride	20.0 mg.	20.0 mg.	40.0 mg.
Phenylephrine hydrochloride	5.0 mg.	5.0 mg.	10.0 mg.
Phenyltoloxamine citrate	7.5 mg.	7.5 mg.	15.0 mg.
Chlorpheniramine maleate	2.5 mg.	2.5 mg.	5.0 mg.

Each teaspoonful (5 ml.) of syrup contains:

Phenylpropanolamine hydrochloride	20.0 mg.
Phenylephrine hydrochloride	5.0 mg.
Phenyltoloxamine citrate	7.5 mg.
Chlorpheniramine maleate	2.5 mg.

Each pediatric formulation contains the following ingredients:	Pediatric Syrup each 5 ml. contains:	Pediatric Drops each 1-ml. dropper contains:
Phenylpropanolamine hydrochloride	5.0 mg.	5.0 mg.
Phenylephrine hydrochloride	1.25 mg.	1.25 mg.
Phenyltoloxamine citrate	2.0 mg.	2.0 mg.
Chlorpheniramine maleate	0.5 mg.	0.5 mg.

ACTIONS: Naldecon is useful for the relief of nasal congestion associated with pollen allergy and minor infections of the upper respiratory tract (the common cold, nasopharyngitis, acute and chronic sinusitis). Naldecon tablets are compounded with half of each ingredient in the outer layer for immediate action and the remainder in the slowly disintegrating core for a sustained effect.

The actions and uses of individual ingredients in the formulation are as follows:

Phenylpropanolamine Hydrochloride

Phenylpropanolamine hydrochloride[1] acts similarly to ephedrine. It is effective orally for the symptomatic control of allergic manifestations, such as perennial hay fever and bronchial asthma. Its action is more prolonged than that of ephedrine, and it is not so apt to produce anxiety complex as is ephedrine.

Phenylephrine Hydrochloride

Phenylephrine hydrochloride[2] is a more powerful vasoconstrictor than synephrine tartrate. When administered orally, it is a vasopressor and relatively nontoxic. The pressor and anti-allergic effects of the drug are produced by oral administration. Therefore, this route may be employed in the treatment of orthostatic hypotension and allergic disorders. The comparatively larger doses required for effective oral treatment are only rarely accompanied by mild gastrointestinal symptoms. These may be avoided by administering the drug after meals.

Phenyltoloxamine Citrate

Phenyltoloxamine citrate[3] is a β-dimethylaminoethyl ether of orthobenzylphenol; as such it belongs to the group of antihistaminics exhibiting the aminoalkyl ether structure. The incidence of side effects is low; at recommended doses, soporific effects occur in less than 7% of patients.

Chlorpheniramine Maleate

Chlorpheniramine maleate[4] has good therapeutic efficacy and lov incidence of side effects. It is comparable in therapeutic efficacy t other antihistaminics although administered in very low dosage.

INDICATIONS: Relief of distressing symptoms of colds and othe upper respiratory infections, acute and chronic sinusitis, hay fever and other pollen allergies:

Rhinorrhea	Lacrimation
Postnasal drip	Sneezing
Nasal congestion	Itching of eyes and nose
Sinus congestion	Head stuffiness

CONTRAINDICATIONS: Sensitivity to any of the ingredients.

PRECAUTIONS: This preparation may cause drowsiness. The patient should be cautioned against engaging in operations requiring alertness such as driving an automobile, operating machinery, etc. Do not exceed the recommended dose unless directed by a physician. Individuals with high blood pressure, heart disease, diabetes mellitus, thyroid disease, glaucoma, peripheral vascular disease or prostatic hypertrophy should use only as directed by a physician.

DOSAGE: This chart represents single dosages for the products listed below. Usual dosage schedule for Naldecon Pediatric Drops, Naldecon Pediatric Syrup and Naldecon Syrup is every 3 to 4 hours, not to exceed four doses in a 24-hour period. For sustained-action Naldecon Tablets, doses should be administered on arising, in midafternoon, and at bedtime.

Single Dosage for...	Pediatric Drops	Pediatric Syrup	Syrup	Tablets
3 to 6 months	1/4 ml.			
6 to 12 months	1/2 ml.	1/2 teaspoonful		
1 to 6 years	1 ml.	1 teaspoonful		
6 to 12 years		2 teaspoonfuls	1/2 teaspoonful	1/2 tablet
over 12 years			1 teaspoonful	1 tablet

REFERENCES:

1. New and Nonofficial Remedies 1955.
2. New and Nonofficial Remedies 1954.
3. A.M.A. Council on Drugs Monograph on Phenyltoloxamine, J.A.M.A. 163:357 (2/2/57).
4. New and Nonofficial Drugs 1959

SUPPLY:

NDC 0015-5600—Naldecon Tablets
NDC 0015-5601—Naldecon Syrup
NDC 0015-5615—Naldecon Pediatric Drops
NDC 0015-5616—Naldecon Pediatric Syrup

For information on package sizes available, refer to the current price schedule.

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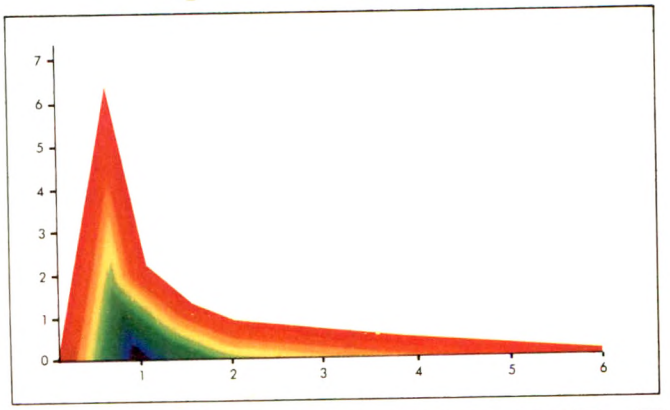
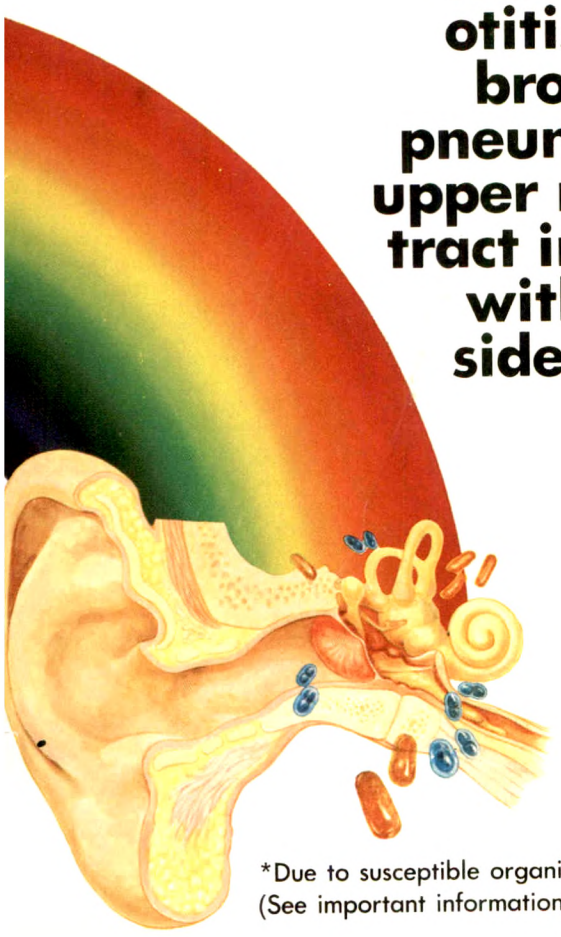
more than just spectrum

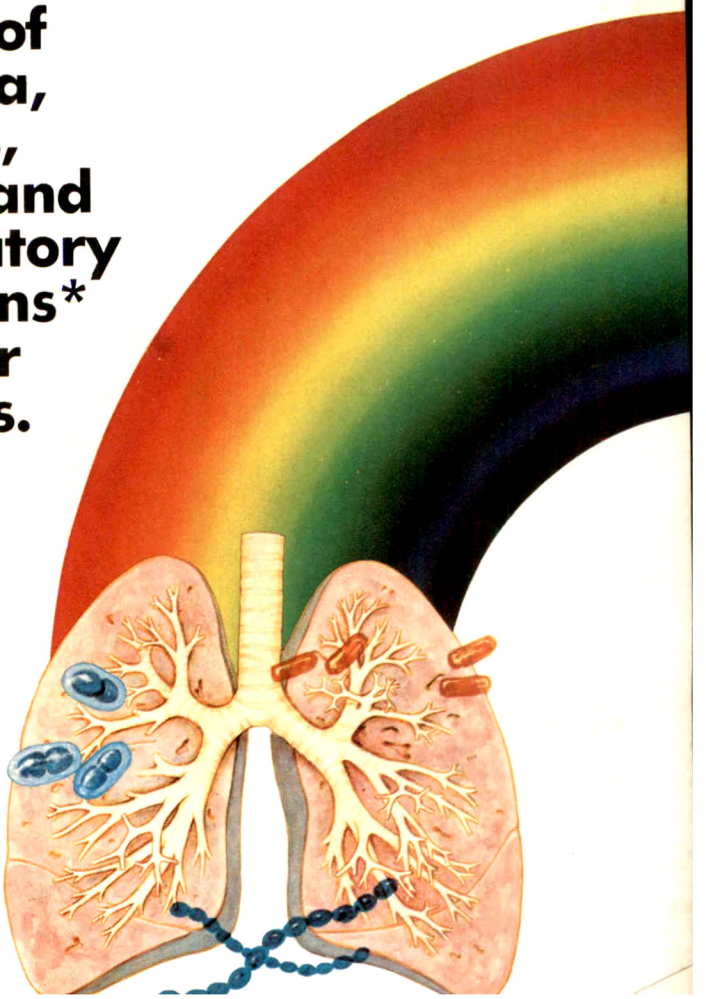


New CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Efficacy proven in the treatment of otitis media, bronchitis, pneumonia and upper respiratory tract infections* with fewer side effects.





*Due to susceptible organisms
(See important information on last page.)

N CYCLAPEN®

(cyclacillin) Tablets/ Suspension

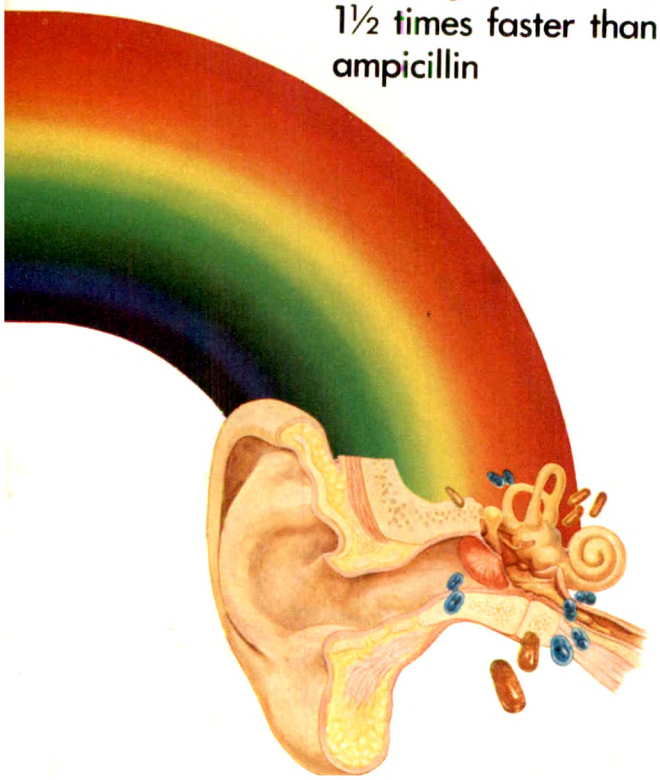
efficacy with fewer sid
ampicillin confirmed i
studies of 2,58

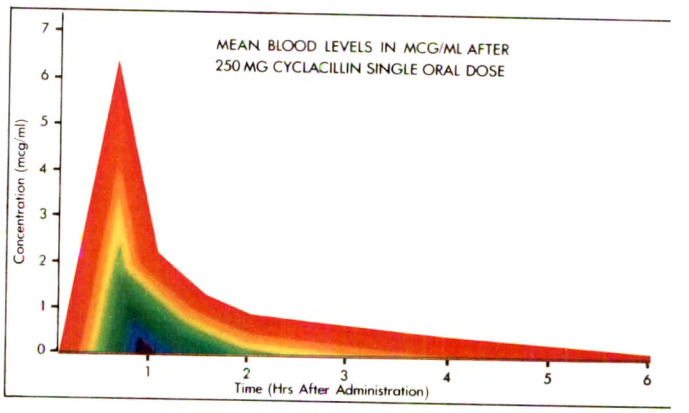
Rapid, virtually complete absorption from GI tract

Rapid onset of action—mean peak serum levels within 30 minutes

Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)

Rapidly excreted unchanged in the urine—1½ times faster than ampicillin





Clinical efficacy of CYCLAPEN® in otitis media†

Causative Organism		No. of Patient
S. pneumoniae	96	82
	95	
H. influenzae	88	96
	85	

% Clinical Response
% Bacterial Eradication

more than just spectrun
in otitis media

*Includes all patients treated. 2,415 evaluated for safety; 1,819 evaluated for efficacy.

†Due to susceptible organisms.

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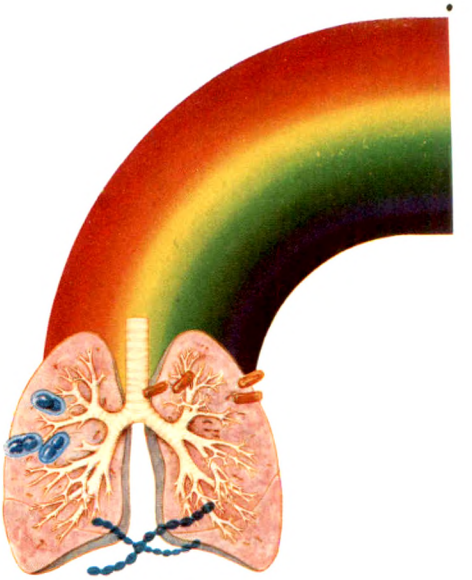
effects than double-blind patients*



ewer side effects with CYCLAPEN® in ouble-blind studies to date[1,2]

Total number of drug-related side effects in all patients	
CYCLAPEN®	128 of 1,286 (10%) of patients
ampicillin	202 of 1,129 (18%) of patients
Difference statistically significant ($P < 0.001$)	

YCLAPEN® (cyclacillin) ffective for otitis media† in children

- Excellent clinical results in eliminating the two most common causative organisms in otitis media
- Significantly lower incidence of diarrhea and skin rash in children treated with CYCLAPEN® Suspension

	diarrhea	rash
CYCLAPEN	9.1%	2.1%
ampicillin	19.2%	5.8%
	$P < 0.001$	$P < 0.03$

In bronchitis, pneumonia and upper respiratory tract infections†

High cure rate with CYCLAPEN®		
Causative Organism	Bronchitis/Pneumonia†	No. of Patients
S. pneumoniae	100	73
	95	
Chronic Bronchitis† (acute exacerbation)		
H. influenzae	92	12
	Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*	
Streptococcal Sore Throat†		
Group A beta-hemolytic Streptococcus	100	44
	86	
% Clinical Response % Bacterial Eradication		

more than just spectrum CYCLAPEN®

(cyclacillin) Tablets/ Suspension

: Gold JA, Hegarty CP, Deitch MW, Walker BR: Double-blind clinical trials of oral cyclacillin and ampicillin, *Antimicrob Ag Chemother* 15:55-58, (Jan.) 1979.

!. Data on file, Wyeth Laboratories.

See important information on next page.)

Wyeth Laboratories
Philadelphia, Pa. 19101

New from Wyeth Laboratories

CYCLAPEN®
(cyclacillin) Tablets/ Suspension

Usual children's dosage: 50 to 100 mg/kg/day in equally space doses, depending on severity.

more than just spectrum in otitis media, bronchitis, pneumonia, and upper respiratory tract infections*

- Rapid, virtually complete absorption from GI tract
- Rapid onset of action—mean peak serum levels within 30 minutes
- Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)
- Rapidly excreted unchanged in the urine—1½ times faster than ampicillin
- Significantly fewer episodes of diarrhea and skin rash than reported with ampicillin in studies to date
- Excellent clinical response and outstanding bacterial eradication documented in double-blind studies involving 2,581 patients
- New CYCLAPEN® Suspension—great-tasting raspberry punch flavor

*Due to susceptible organisms.

How Supplied

CYCLAPEN® (cyclacillin) tablets:
250 mg scored tablets
500 mg scored tablets

Indications

Cyclapen® (cyclacillin) has less in vitro activity than other drugs in the ampicillin class of antibiotics and its use should be confined to the indications listed below.

Cyclapen® is indicated for the treatment of the following infections:

RESPIRATORY TRACT

Tonsillitis and pharyngitis caused by Group A beta-hemolytic streptococci

Bronchitis and pneumonia caused by *S. pneumoniae* (formerly *D. pneumoniae*)

Otitis Media caused by *S. pneumoniae* (formerly *D. pneumoniae*) and *H. influenzae*

Acute exacerbation of chronic bronchitis caused by *H. influenzae**

*Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*.

SKIN AND SKIN STRUCTURES (integumentary) infections caused by Group A beta-hemolytic streptococci and staphylococci, non-penicillinase producers.

URINARY TRACT INFECTIONS caused by *E. coli* and *P. mirabilis*. (This drug should not be used in any infections caused by *E. coli* and *P. mirabilis* other than urinary tract infections.)

NOTE: Cultures and susceptibility tests should be performed initially and during treatment to monitor the effectiveness of therapy and the susceptibility of bacteria. Therapy may be instituted prior to the results of sensitivity testing.

Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to penicillins.

Warnings

CYCLACILLIN SHOULD ONLY BE PRESCRIBED FOR THE INDICATIONS LISTED IN THIS INSERT.

CYCLACILLIN HAS LESS *IN VITRO* ACTIVITY THAN OTHER DRUGS OF THE AMPICILLIN CLASS ANTIBIOTICS. HOWEVER, CLINICAL TRIALS HAVE DEMONSTRATED THAT IT IS EFFICACIOUS FOR THE RECOMMENDED INDICATIONS.

SERIOUS AND OCCASIONAL FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING PENICILLIN.

ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL ADMINISTRATION, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE ARE REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY REACTIONS WHO EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH A CEPHALOSPORIN. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE ABOUT PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY SHOULD BE INITIATED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

PREGNANCY: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to ten times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cyclacillin is administered to a nursing woman.

Adverse Reactions

The oral administration of cyclacillin is generally well tolerated.

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asth fever, or urticaria.

The following adverse reactions have been reported with the use of cy diarrhea (in approximately 1 out of 20 patients treated), nausea and v (in approximately 1 in 50), and skin rash (in approxmately 1 in 60). instances of headache, dizziness, abdominal pain, vaginitis, and urtica been reported. (See WARNINGS)

Other less frequent adverse reactions which may occur and that ha reported during therapy with other penicillins are: anemia, thrombocy thrombocytopenic purpura, leukopenia, neutropenia and eosinophilia reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been re

Dosage and Administration

INFECTION*	ADULTS	CHILDREN
		Dosage should not in a dose higher th for adults.
Respiratory Tract		
Tonsillitis & Pharyngitis**	250 mg q.i.d. in equally spaced doses	body weight <20 lbs) 125 mg q.i equally spaced dos body weight >20 lbs) 250 mg q.i equally spaced dos
Bronchitis and Pneumonia		
Mild or Moderate Infections	250 mg q.i.d. in equally spaced doses	50 mg/kg/day q. equally spaced dos
Chronic Infections	500 mg q.i.d. in equally spaced doses	100 mg/kg/day q equally spaced dos
Otitis Media	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/kg/ equally spaced dos pending on severity
Skin & Skin Structures	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/kg/ equally spaced dos pending on severity
Urinary Tract	500 mg q.i.d. in equally spaced doses	100 mg/kg/day in e spaced doses.

*As with antibiotic therapy generally, treatment should be continued minimum of 48 to 72 hours after the patient becomes asymptomatic c evidence of bacterial eradication has been obtained.

**In infections caused by Group A beta-hemolytic streptococci, a minim 10 days of treatment is recommended to guard against the risk of rhei fever or glomerulonephritis.

In the treatment of chronic urinary tract infection, frequent bacteriolog clinical appraisal is necessary during therapy and may be required for s months afterwards.

Persistent infection may require treatment for several weeks.

Cyclacillin is not indicated in children under 2 months of age.

Patients with Renal Failure

Based on a dosage of 500 mg q.i.d., the following adjustment in d interval is recommended:

Patients with a creatinine clearance of >50 ml/min need n age interval adjustment.

Patients with a creatinine clearance of 30-50 ml/min should recei doses every 12 hours.

Patients with a creatinine clearance of between 15-30 ml/min receive full doses every 18 hours.

Patients with a creatinine clearance of between 10-15 ml/min receive full doses every 24 hours.

In patients with a creatinine clearance of ≤10 ml/mi serum creatinine values of ≥ 10 mg %, serum cyclacillin levels are r mended to determine both subsequent dosage and frequency.

CYCLAPEN® (cyclacillin) fo oral suspension
125 mg per 5 ml:
100 ml and 200 ml bottles
250 mg per 5 ml:
100 ml and 200 ml bottles

Wyeth Laboratories
Philadelphia, Pa. 19101

The Critical Academic Mass

Intuition suggests that increasing departmental size might affect individual research productivity by enhancing opportunities to share ideas, responsibilities, and facilities. If so, the effect could either extend indefinitely (ie, "the bigger the better") or reach a plateau that indicates the point of maximum profitable interaction. In the United States, pediatric full-time faculty rosters presently range from three to 141, according to data provided by 116 department chairmen. A test of these concepts thus requires only a reasonable, quantitative estimate of productivity. We chose to count publications and presentations at the annual meetings of the Society for Pediatric Research and the American Pediatric Society (APS/SPR). Forty-eight journals were searched for articles published between July 1, 1976 and June 30, 1978 that originated from the 116 departments studied, and the programs of the 1977 and 1978 APS/SPR meetings were scanned for articles accepted for presentation. The journals selected included four that deal with pediatrics *(The American Journal of Diseases of Children, The Journal of Pediatrics, Pediatrics,* and *Pediatric Research)*, four that include both pediatric and adult medical research *(The Journal of Clinical Investigation, The Journal of Laboratory and Clinical Medicine, The New England Journal of Medicine,* and *Metabolism)*, *Science*, and 39 subspecialty journals. All articles from these sources were assigned to the departments with which their authors were associated. Some were credited to more than one department. Each list of departmental publications was divided by the number of full-time faculty; the result was designated as the departmental per capita productivity index (PI). Separate indices were calculated for general and subspecialty papers. The sample comprised a total of 4,198 items: 687 presentations, 1,660 articles in general research journals, and 1,851 articles in subspecialty journals.

Per capita productivity indices so derived are clearly different from those that would result from counting individual bibliographies within each department. The latter figures, however, would exceed the total number of publications because of the phenomenon of multiple authorship. A random sample of 100 papers gave an average of 3.6 (± 0.23) authors per paper; the summation of individual bibliographies would, therefore, suggest a total research output several times larger than life. An unfortunate aspect of this enumerative approach is the absence of qualitative evaluation. We hope that the efforts of editors, reviewers, and program chairmen, together with the large sample size, may have engendered a reasonable correspondence between quality and quantity. The limitation of the analysis to American departments, publications, and meetings was dictated by available clerical resources.

In research as well as in teaching and patient care, major contributions are made by those who hold qualified or "clinical" appointments. However, the time invested and the responsibilities assumed by such faculty members are so extremely variable that it seemed impractical to include them in the rosters on which this study was based.

The Table gives the results. The median departmental size was 30 members. Both general and subspecialty indices were much greater in departments with 30 or more full-time members. The difference was more noticeable for subspecialty than for general items. Above and below the median, there was no correspondence between departmental roster and PI. Nine departments had PIs of 2.0 or more; these were evenly distributed without relationship to size. They were (with rosters in parentheses): University of Vermont (seven), Penn State (14), University of Illinois (21), State University of New York, Upstate Medical Center (24), Yale (44), Washington University (46), University of California, San Francisco (52), University of Washington (60), and Harvard (141). Penn State and Harvard had PIs of 3.0.

Insofar as these results accurately describe productivity, the advantage of increasing departmental size appears to be reached when the roster is 30. Departments larger than this have larger total research outputs, of course, but no greater per capita efficiency. Evidently there is a limit to the amount of profitable interaction

Per Capita Productivity (PI) Related to Department Size

Roster Size (n)	PI, General (SE)	PI, Specialty (SE)	PI, Total (SE)	PI > 2.0
<30(57)	0.37(0.07)	0.20(0.03)	0.57(0.09)	4
>30(59)	0.58(0.05)*	0.45(0.04)†	1.03(0.08)†	5

*$P < .02$.
†$P < .001$.

between any one person and his colleagues. Responsibilities for patient care, teaching, administration, and advocacy might be lightened in larger departments; if so, any enhancement of research activity thus engendered apparently also reaches a plateau at 30. The phenomenon of extremely high productivity by some persons and small groups of investigators is well known and would be expected to introduce wide variability about the means shown in the Table; such is indeed the case. For statistical purposes, standard errors are given; the standard deviations (standard error $\times \sqrt{n}$) are relatively large, and approximate the means themselves. The wide distribution of PIs greater than 2 shows that exceptionally productive persons and groups are capable of overcoming the statistically significant effect of departmental size.

Patient care, teaching, and advocacy are equally important functions not susceptible to the simple quantitation offered here for research publications. If there is a critical mass for these activities, its definition will require the development and application of evaluative techniques not presently available.

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Commentary on Immunization

Schedules for immunization against childhood infections have been issued periodically by select committees from the American Academy of Pediatrics and the Public Health Service. These schedules are especially appropriate for public health clinics, but the private physician may have reasons of his own to set up alternative patterns.

In *The Hazards of Immunization*, Wilson[1(p2)] defended freedom to oppose majority opinions and believed that long-adopted practices should periodically be critically scrutinized "lest the accumulated weight of precedent is allowed to obscure the need for their discontinuance."

Immunizations have greatly decreased the incidence of several common diseases in childhood; there is the possibility that some have only been deferred to adult years. The effectiveness of each agent cannot be compared directly with others, nor can any new agent be instantly accepted because of its resemblance to one that has been proved effective. Moreover, no vaccine should be inviolate of scrutiny and reevaluation.

Smallpox vaccine, the progenitor of live virus vaccines (LVVs), has the incomparable advantage that the resultant vaccine vesicle demonstrates the establishment of the benign protective infection. This is not true of current LVV, where resistance is demonstrated only by extensive experience or serological tests. One may be encouraged to believe that LVV agents should rival the duration and effectiveness produced by actual disease, but even the immunity that follows smallpox vaccination is not invariably prolonged; revaccination is required after one to three years, and mild forms of the disease may occur later on.

The conquest of diphtheria was accelerated by the discovery that horses could be immunized with modified toxin and that their blood serum could be used for prevention and treatment of the disease. This potent antitoxin was suspected to be useful against other infections although this proved to be untrue. An antitoxin against many other infections was anticipated but was not accomplished except to a limited extent. The treatment of diphtheria by antitoxin led to the use of modified toxin for childhood immunization.

The Schick test was first designed to demonstrate the adequacy of antitoxin at a time when it was customary to give daily doses of antitoxin in treatment. Later, this test served to demonstrate successful immunization. The Schick test has now been abandoned, which is unfortunate because it not only demonstrates the immunity of the patient given toxoid but also demonstrates his ability to respond to an antigenic stimulus.

Wallgren[2] stated that the presence of transplacental diphtheria antibodies interferes with the antibody response to toxoid. This is somewhat erroneous since booster injections given when antitoxin is present will cause a great increase in antitoxin levels, but it is possible that administration of toxoid later than extremely early in infancy might encourage a more durable immunity. However, immunization in early infancy is chosen to select the most accessible time to the patient.

Live virus vaccines, as in smallpox, succeed only to the extent that they produce subclinical infection. Immunization must usually be deferred until the disappearance of transplacental antibodies that could interfere.

POLIOMYELITIS VACCINE

Live virus poliomyelitis vaccine seems to be an exception for oral poliovirus vaccine (OPV) (Sabin live virus) is usually given at 2 or 3 months of age along with diphtheria and tetanus toxoids in combination with inactivated pertussis vaccine (DTP).

A recent observation suggests that OPV and DTP should not be given coincidentally. Four cases occurred in Britain[3] in which DTP and OPV given at the same time were followed by paralysis in 14 to 17 days. In all four, the extremity injected with DTP was the site of paralysis; in two, it was also accompanied by weakness elsewhere. Paralysis follows OPV only once in 2 to 5 million doses, but is it logical to combine it with another vaccine that is known to be a provocative agent? During poliomyelitis epidemics, it was observed that paralysis seemed to be precipitated by the injection of DTP, and weakness usually occurred in the extremity injected with DTP. With the prevailing immune protection of the population, it might be appropriate to defer OPV to 6 or 8 months of age instead of insisting on combining it with DTP in early infancy, avoiding a coincidental provocative agent.

INACTIVATED POLIOVIRUS VACCINE (IPV)

Inactivated poliovirus vaccine (Salk) does not produce subclinical infection, and transplacental antibodies do not interfere with the immune response. Salk and Salk[4] have stated that paralysis because of OPV now exceeds that caused by wild virus. Although this may be true, the numbers are extremely small: seven cases of poliomyelitis were reported in 1978, five of which were associated with OPV (MP Pollack, MD, written communication, May 9, 1979). When Salk's IPV was introduced in 1955, more than 100 paralytic cases were found to be due to the presence of live virus. Although the number of paralytic cases in the United States decreased after the introduction of IPV in the years 1957 to 1959, Wallgren[2] stated that a coincidental decline also occurred in Sweden where the vaccine was not yet used. Currently, it is used in Sweden with apparently good effect. In contrast to OPV, IPV requires repeated boosters, is more difficult to administer, does not afford as great a degree of herd immunity, and cannot be used for containment of an epidemic.

PERTUSSIS VACCINE

Pertussis vaccine was introduced about 1936; however, since at least 1900, there has been a steady decrease in mortality from this disease. With the advent of this vaccine, the decline has continued but is now piously attributed to vaccination. Mortality is probably the best statistical evidence of actual occurrence because morbidity is not so well reported. This continuous decline in mortality may be due to many factors, including better protection from exposure, improved nutrition, or, as occurs with many pathogens, a diminished virulence of the organism.

Frequent objections to the use of pertussis vaccine began to appear in the British literature about 1974. Stewart[5] has been a vociferous opponent and stated that DTP has little protective effect against whooping cough and causes innumerable adverse reactions that constitute a substantial risk. The risks are convincingly attributed to the pertussis component.[1(p263),6]

These opinions led to an editorial in *Lancet*[7] and a succinct review in the *New England Journal of Medicine*.[8] In the United States, there has been less concern about pertussis vaccine although severe adverse reactions were reported as early as 1948.[9] Barkin and Pichichero[10] in a review of 1,232 patients found a notable incidence of reactions although without the convulsions and encephalopathy that had been noted in more extensive studies.[11-13] In both Britain and the United States, public health authorities have moved furiously in defense of the vaccine. The British Joint Committee on Vaccination and Immunisation has had a survey under way since 1976 (unpublished data, September 1977) to determine the frequency of complications, but it is their unanimous opinion that the vaccine's use should be continued.

Edsall[14] commented that alarm over the publicity of sequellae in Britain has resulted not only in the decreased immunization against pertussis but has also regrettably interfered with the acceptance of other vaccines. He believed that these alarmist views have not been supported by facts and that the lack of acceptance of vaccination has been accompanied by an increase in the incidence of whooping cough. He did agree that an entirely different vaccine with less toxicity and more dependable protective effect is desirable.

Currently, a great increase in whooping cough has been reported in Britain, after opposition to vaccine and public rejection (about 1974). If the present epidemic is due to vaccine nonuse, this should be evidenced in children younger than 4 to 5 years of age and best indicated by mortality that is greatest in this age group. Such data together with morbidity in older children might defend the vaccine in regard to its effectiveness and support its worth.

There may be some reluctance to report reactions for fear of legal reprisals. The lack of reliable data about the incidence and severity of reactions might be compared with the meticulous surveillance of OPV since its introduction. A calculated risk factor of 1/4 or 5 million doses is believed to be acceptable with OPV. This is much less than the anecdotal estimates of severe reactions because of pertussis vaccine.

PERTUSSIS VACCINE UNIQUE

This vaccine is unique in that it is the only current vaccine consisting of a suspension of killed bacteria that is credited with effective and prolonged immunity. Similar vaccines consisting of killed bacterial suspensions are notoriously less dependable, less accepted, and require frequent boosters, eg, typhoid, plague, cholera, paratyphoid (which has been abandoned). Pertussis vaccine is a poor antigen so that the agglutination response may not measure its true protective value. It is impossible to compare the usefulness and safety of this vaccine with those of such antigenicity as the toxoids of diphtheria and tetanus.

If pertussis vaccine were proposed now for initial approval, it is questionable whether it would be endorsed; for that matter, Jenner would certainly have difficulty in receiving initial approval of his vaccine! It would be a

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shattering proposal that pertussis vaccine be impetuously abandoned. One need neither go this far nor assert that it has no beneficial effect. However, studies are in order both here and abroad for careful surveillance of risk and effectiveness; there may be differences in populations and in vaccines. A vaccine with less toxicity and more dependable protective effect has long been sought, and the search should continue.

MEASLES VACCINE

Inactivated measles virus vaccine was considered appropriate when it was introduced but was a near disaster. The effectiveness of attenuated live virus measles vaccine has been conclusively demonstrated, and this produces a benign infection that provokes long-standing immunity. Transplacental antibodies interfere, for measles virus is exquisitely sensitive to extremely small amounts of antibody. Thus, it is appropriately deferred until 15 months of age when all transplacental antibodies have disappeared.

RUBELLA AND MUMPS VACCINE

Rubella and mumps vaccine, used for less than ten years, have not been completely studied regarding their present and remote value. Rubella is a common, mild disease of childhood with few important complications; epidemics recur about every seven years, with the result that about 85% of adults are immune. The only major concern is infection during pregnancy, which might occur among the 15% nonimmune female population, because of the well-known devastating effects on the fetus. Immunization of both boys and girls at 15 months of age is officially recommended in the United States and is frequently required before first school attendance. A somewhat unrealistic hope is that herd immunity of both boys and girls will protect their mothers who might be susceptible and pregnant. An important and thus far unanswered question is whether immunization at 15 months of age will protect girls when they reach their childbearing years or if this immunity will lapse, as suggested by Horstmann et al,[15] who agreed with other authorities that the latest vaccine (RA27/3) is much better than previous vaccines.[16] Revaccination of girls at 11 to 12 years might be useful but is unlikely to be effectively carried out. But why not adopt the British scheme of vaccinating only the girls during early adolescence, with greater assurance of their immunity at childbearing age?

Mumps immunization, a latecomer, is advocated for both boys and girls. Complications in childhood are rare and risks are so minimal that there is little reason why all children should be immunized at 15 months, although some states require it before first school attendance. The CNS symptoms often reported as meningoencephalitis usually consist only of benign meningitis, which occurs in at least 50% of all mumps cases and probably occurs much more frequently than it is diagnosed[17]; Postinfectious encephalitis, a serious disease, is extremely rare (1/6,000). Deafness, frequently stated as a risk of mumps, occurs rarely (1/15,000) and is usually unilateral.[17] Orchitis practically never occurs before adult years, but it is much dreaded by men because of its painful course and the overstated belief that it will induce impotence or sterility. However, it is an open question whether vaccination at 15 months will protect the boy during his adult years. Would it not be more reasonable to immunize only boys during early puberty?

Probably the greatest reason for acceptance of rubella and mumps immunization is that they can be given in combination with measles (MMR), thus avoiding frequent patient visits. This, too, appeals to public health clinics, but there are other good reasons for frequent visits to the pediatrician during preschool years.

It is impossible to extrapolate from successful vaccination against diphtheria, tetanus, poliomyelitis, and measles to some other vaccines in common use or to predict the success of each newly developed one. They are not the answer to every disease, and their benefits and risks require careful evaluation. To equate unnecessary and perhaps frivolous immunizations with those of indisputable value is to denigrate those that are useful and to discourage public acceptance of all vaccines. The untoward experiences with inactivated measles vaccine and the swine influenza episode have not enhanced public confidence in routine immunization. Vaccinations should be divided carefully into those that are successful and necessary (poliovirus, diphtheria, tetanus, and measles) so as to be almost obligatory and those others that parents or physicians may select.

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San Francisco, CA 94143

References

1. Wilson GS: *The Hazards of Immunization*. London, The Athlone Press of the University of London, 1967.
2. Wallgren D: Vaccination in childhood. *Triangle* 4:49-54, 1958.
3. Collingham KE, Pollock TM, Roebuck M: Paralytic poliomyelitis in England and Wales 1976-77. *Lancet* 1:976-977, 1978.
4. Salk J, Salk D: Control of influenza and poliomyelitis with killed virus vaccines. *Science* 195:834-847, 1977.
5. Stewart GT: Vaccination against whooping cough: Efficacy vs risks. *Lancet* 1:234-237, 1977.
6. Burnet M, White DO: *The Natural History of Infectious Disease*. London, Cambridge University Press, 1972, p 170.
7. Whooping cough vacillation, editorial. *Lancet* 2:71, 1977.
8. Grady GF, Wetterland SB: Pertussis vaccine: Reasonable doubt. *N Engl J Med* 298:966-967, 1978.
9. Byers RK, Moll FC: Encephalopathies following prophylactic pertussis vaccine. *Pediatrics* 1:437-456, 1948.
10. Barkin RM, Pichichero ME: Diphtheria, pertussis, tetanus vaccines: Reactogenicity of commercial products. *Pediatrics* 63:256-260, 1979.
11. Strom J: Further experience of reactions especially of cerebral nature in conjunction with triple vaccine: A study based on vaccinations in Sweden 1959-1965. *Br Med J* 4:320-323, 1967.
12. Linneman CC, Parten PH, Perlstein PW, et al: Pertussis: Persistent problems. *J Pediatr* 85:589-591, 1974.
13. Kolenkampff M, Schwartz JS, Wilson J: Neurologic complications of pertussis inoculation. *Arch Dis Child* 49:46-49, 1974.
14. Edsall G: Pertussis vaccine. *N Engl J Med* 283:771-778, 1978.
15. Horstmann DM, Lieberhaber H, Lebouvier CL, et al: Rubella: Reinfection of vaccinated and naturally immune persons exposed to an epidemic. *N Engl J Med* 283:771-782, 1970.
16. Horstmann DM: Neutralizing and hemagglutination antibodies to rubella virus as an indicator of protection in vaccinees and natural immune individuals. *J Infect Dis* 138:877-883, 1979.
17. Hoeprich PD: *Infectious Diseases*. Hagerstown, Md, Harper & Row Publishers Inc, 1977, p 623.

Impact of Mass Media on Adolescent Sexual Behavior

The Chicken or the Egg?

Although adolescent sexual behavior has become a focal point for debate among family members, educators, and health providers, the percent of young people who have their first intercourse experience in adolescence has not increased dramatically in the past decade.[1] The mass media has reflected the increased awareness of adolescent sexual behavior. One important issue that has arisen is whether certain of the attitudes and behaviors surrounding teenage sexuality are started by the media or if the media merely reflects the beliefs and attitudes already held in a community. By assessing the effect of the media on changing belief systems as well as on education of populations in such sexually related areas as venereal disease control, one could analyze the potential impact of publicity on adolescent sexual behavior.

The general conclusion of investigators in the field of mass communication is that the messages in the media merely reinforce attitudes that are already held.[2] Earl Ubell,[3] science editor for the Columbia Broadcasting System, has described the capability of the media as allowing people to become informed about the existence of an item or concept but not imparting sufficient details to lead to changes in behavior.

THE POTENTIAL ROLE OF MASS MEDIA

There are data to support the belief that mass media reporting may reinforce behavior that is already present but there is no evidence that mass media introduces the idea of premarital intercourse to young people. Motivation for a sexual behavior in a given adolescent is influenced by a series of factors. These include goals that make the action attractive or unattractive to an individual, as well as external and environmental influences that favor or oppose the behavior. If mass media techniques are to be adapted to health education to motivate adolescents to seek care for sexually related conditions, then factors which must be present include: (1) a belief that many individuals are susceptible to the illness (usually because of the presence of a sign or symptom); (2) a belief by individuals that the condition or disease is serious; and (3) a perception by individuals that they will benefit by changing behaviors.

Mass media can and should be used for adolescent health informational purposes. However, it must be appreciated that teenagers often engage in sexual behaviors for individual reasons that are not apt to be altered by an encounter with new information. Mass media can only be effective when there is little or no resistance to the adoption of new views.[3] When mass media do alter attitudes, the changes occur either in a small percent of the population at a given time or slowly over a long period. Commercial advertisers seek to influence the brand selection of sufficiently large numbers of consumers to make the advertising economically feasible. Such advertising techniques can reach individuals who are ready to buy an item but are searching for information about where to buy or selecting among similar products. Programs that try to modify a behavior rather than offering information should use surveys to test the "messages" and the potential impact of the programming. If such programs are to be used for health education, then they should not represent the only technique used in reaching the market population.

If mass media are to be used for the advancement of certain concepts or practices in preventive medicine, it is incumbent on the health provider to propose the desired content, potential outcome, and impact on public health. There would be little difficulty in enlisting members of the media to carry out such programming. Through the use of newspapers, magazines, radio, and television, an attempt should not be made to convince the public of ideas for which there is little scientific merit. If mass media is to be part of a campaign to inform adolescents about the problems of venereal disease, it is incumbent on public health workers to understand the limitations of the approach and to provide specific tasks for the media to perform. A venereal disease control program using mass media is suitable only if the social scientist demonstrates that the dissemination of information can play an important role in curbing the behavior that spreads the disease. The responsibility for designing such a program should rest in part with the health professional. The media can relay information to achieve the goals of alerting and informing an adolescent audience only after the other requirements are met by the health professional.[3]

INCREASING KNOWLEDGE AND CHANGE IN ATTITUDES OR BEHAVIOR

Transmitting information may increase knowledge but may have little effect on adolescent attitudes or sexual behavior. The concern on the part of adults regarding teenage sexuality is usually only focused on

the behavior. It is assumed that knowledge (or lack of it) plays a major role in adolescent sexual behavior.

However, recent studies of the effects of sex education courses on sexual attitudes and behaviors have indicated surprising results. A sex education course for eighth-grade adolescents had little influence on attitudes but did increase the tolerance for the sexual behavior of other students.[4] A study of the impact of sex education on a population of college students showed no relationship between those who participated in a course and their reported premarital sexual behavior.[5] There was also no difference in contraceptive behavior or in coital patterns between those college students who reported having had instruction in the use of birth control and those with no instruction. Similarly, no difference in behavior was noted between those who had different types of teachers or those who had courses in different years of school. Most surveys of the impact of sex education courses look only at changes in attitudes and rarely at changes in subsequent sexual behavior.[6]

There is certainly a major role for the media in education.[7] Although studies have been conducted that elucidate techniques that can be used to maximize learning capabilities, there remains a lack of thoughtful programming specifically designed for educational purposes. There is a need for continuing research on reactions to material by adolescents rather than relying solely on adult estimates of what the adolescents' reactions are likely to be. In an attempt to attract a large viewing, reading, or listening audience, media programmers often design the content of the show to be appealing to the least sophisticated viewers. Rapid-action sequences are frequently adopted rather than slower-paced scenes that might allow time for thoughtful reaction.[8]

Printed material requires separate comment. The comic book format, a style used in mass media literature, has been used by health educators because of the acceptability of visual material to many teenagers. This particular medium deemphasizes the format of uninterrupted paragraphs of written material. The "mediazation" of health educational materials has been well received by many teenagers, particularly when the graphic materials depict teenagers rather than adults and are representative of a cross-section of ages and ethnic groups.[9] The effort to incorporate practices used by mass media into health education is one of the major advances in health education. When the content is accurate and timely and is presented in a format that will have greater patient acceptability, it will certainly complement other efforts by health educators in transmitting factual, relevant material to the teenage consumer.

Some individuals maintain that the presence of sexually related materials in the press encourage overt sexual behavior, erode authority, and "encourage irresponsibility in others."[10] The current posture of the American Academy of Pediatrics regarding the violent content of television programs and excessive exposure of small children to advertising has been to try to limit both by influencing public policies through its youth advocacy role.[11] For the adolescent audience, concern has been expressed about the sex stereotyping that many television programs demonstrate as well as the unilateral presentation of views on such topics as teenage pregnancy, contraception, or abortion. However, it may be an error to extrapolate from the presumed effects of mass communication on the behavior of small children to the behavior of adolescents. Teenagers with normal personality development are less likely to be influenced in their behavior by external influences beyond their family, friends, and community than are younger children. To analyze the potential or real impact of the media on adolescent sexual behavior, an understanding of the development of adolescent decision making is necessary. The process of reasoning by which a teenager analyzes information, which results in a personal choice of a sexual behavior, has been linked with the individual's developmental stage of moral thinking.[12] The cognitive structure into which an adolescent places experiences is a major determinant of social behavior. The development of "abstract" thinking from "concrete" thinking is a normal cognitive milestone of midadolescence. Since discussion about decisions regarding sexuality have only recently been encouraged in our society, teenagers have little opportunity to practice high levels of moral reasoning. Adults often apply low levels of moral reasoning when discussing sexual decision making with teenagers.

It seems that choices regarding patterns of adolescent sexual behavior are independent of the effects of mass media. If adolescent sexual behavior is viewed as an "egg," then mass media can become the "nest" that nurtures the "egg" but cannot change its contents once the "egg" is formed.

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References

1. Zelnick M, Kantner JF: Sexual and contraceptive experience of young, unmarried women in the United States, 1976 and 1971. *Fam Plann Perspect* 9:55-71, 1977.
2. Klapper JT: *The Effects of Mass Communication*. New York, The Free Press, 1960.
3. Ubell E: The responsibility of the mass media in the control of sexually transmitted diseases: A hammer without a nail. *Bull NY Acad Med* 52:1019-1036, 1976.
4. Parcel GS, Luttman D: The effects of a sex education course on young adolescents' sexual attitudes. Presented at the annual meeting of the Ambulatory Pediatric Association, Atlanta, 1979.
5. Spanier GB: Sex education and premarital sexual behavior among American college students. *Adolescence* 13:659-674, 1978.
6. Cohen CI, Cohen EJ: Health education: Panacea, pernicious or pointless? *N Engl J Med* 299:718-720, 1978.
7. Ubell E: Preventive medicine and federal health policy. *Coll Prevent Med Newsletter* 17:1-7, 1976.
8. Singer JL, Singer DG: Television for children: Effects on learning. *Science* 203:400, 1979.
9. Committee on Adolescence: *Selected References on Low Cost Sex Education Publications for Teenage Youths*. Evanston, Ill, American Academy of Pediatrics, 1974.
10. Ellison SE, King A, Peel J, et al: Sexual pressures on children. *Br Med J* 2:353, 1978.
11. Feinbloom RI: TV update. *Pediatrics* 62:428-431, 1978.
12. Wilson WC: Adolescent moral development and sexual decision, in *Sex and Youth: A Symposium*. Chicago, American Library Association, 1978.

Marginal Comments

Serum 1,25-Dihydroxyvitamin D Levels in Normal Children and in Vitamin D Disorders

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• Using a precise assay for 1,25-dihydroxyvitamin D in serum, the levels in 103 children, aged 13 months to 16 years, were found to be 43 ± 2 pg/mL (mean ± SE). This value is higher than reported values in adults and in neonates. Age-related changes in 1,25-dihydroxyvitamin D levels during childhood were also evident. Older children have significantly higher levels than children < 11 years, possibly indicating changes with puberty and the adolescent growth spurt. The values were significantly reduced in childhood uremia (13 ± 5 pg/mL), in hypoparathyroidism (16 ± 1 pg/mL), and in children with Fanconi's syndrome. Treatment with oral calcitriol in these three groups of patients led to increased serum levels.

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Vitamin D requires two separate hydroxylations, first at carbon 25 occurring in the liver and later at carbon 1 in the kidney, to yield the biologically active metabolite, 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). This metabolite has notable antirachitic activity and stimulates the intestinal absorption of calcium and phosphorus.[1] Since this compound also leads to the release of calcium and phosphorus from bone,[2] its major biological role may be the maintenance of normal plasma concentrations of these divalent minerals. In children, disorders of bone mineralization may be related, in part, to decreased serum levels of 1,25-$(OH)_2$D, particularly as the rapid turnover of bone and growth demands of childhood requires net positive calcium and phosphorus balance.[3] The development of a highly sensitive and precise method of determining the serum levels of 1,25-$(OH)_2$D[4,5] permits direct measurements of this metabolite in children with disorders of calcium and phosphorus metabolism.

See p 140.

This study examines the concentrations of 1,25-$(OH)_2$D in normal children according to age, and it compares these values to previously published data in neonates and adults.[5,6] Comparisons of normal values with those found in children with hypoparathyroidism, uremic osteodystrophy, and Fanconi's syndrome were also made.

MATERIALS AND METHODS

An extra 7-mL aliquot of blood was removed from children undergoing venipuncture for routine laboratory studies prior to elective surgery (tonsillectomy, herniorrhaphy, or strabismus repair). These children, aged 13 months to 16 years, were healthy and remained anonymous; hence, they could not be further identified. Informed consent was obtained from the parents of these control subjects, using a protocol approved by the Human Subjects Committees in both Madison, Wis, and New York. Samples were obtained in each month of the year. Serum was stored at −20 °C until analyzed, and samples sent from New York were shipped in dry ice and were received in the frozen state. Samples were also obtained from patients with the following disorders: infantile nephropathic cystinosis, autosomal dominant Fanconi's syndrome,[7] Lowe's syndrome, idiopathic hypoparathyroidism that was identified by absent or diminished parathyroid hormone (PTH) levels[8] (13 cases), and uremic osteodystrophy (nine cases). Samples were also obtained in several patients after therapy with oral calcitriol (1,25-$(OH)_2$D) for at least several weeks. These samples were taken at four to six hours after the preceding dose of calcitriol.

Serum levels of 1,25-$(OH)_2$D were measured by the method of Eisman et al.[4,5] This method involves a specific extraction procedure in methylene chloride and a competitive binding assay using intestinal cytosol from rachitic chicks. Assays were always performed in parallel with known

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internal standards to confirm reproducibility of the assays. The precision of this assay is ±2 pg/mL. Recoveries were determined using internal standard 1,25-$(OH)_2$-[^{3}H]D as previously described.[4,5] The calcitriol used for therapy was administered as a single morning dose.

Statistical significance of differences between groups was determined by Student's t test. Correlation coefficients were calculated by the Pearson's product moment formula.

RESULTS

Serum 1,25-$(OH)_2$D Levels in Normal Children

Shown in Fig 1 are the levels of 1,25-$(OH)_2$D found in 103 healthy children. The mean value obtained in 71 children from Wisconsin was 44 ± 3 pg/mL (mean ± SE), which is not different from the level of 41 ± 3 pg/mL found in 32 children from New York City. The value found in 50 girls was 44 ± 3 pg/mL compared with 39 ± 4 pg/mL in 53 boys. The overall mean level in the 103 children was 43 ± 2 pg/mL, with a range of 11 to 111 pg/mL. The relationship between serum 1,25-$(OH)_2$D levels and age has a linear correlation coefficient of $r = .418$ ($P < .001$), indicating that these levels increase with age proceeding from chilhood into adolescence. No seasonal differences were apparent. The (±SE) values at various ages were as follows: 1 to 2 years, 35 ± 2 pg/mL (n = 7); 3 to 4 years, 35 ± 2 pg/mL (n = 17); 5 to 6 years, 37 ± 4 pg/mL (n + 20); 7 to 8 years, 41 ± 4 pg/mL (n = 19); 9 to 11 years, 42 ± 8 pg/mL (n = 11); and 12 to 16 years, 55 ± 2 pg/mL (n = 29). The value in 74 children less than 12 years of age was 38 ± 3 pg/mL, which is significantly lower than the value of 55 ± 2 pg/mL in adolescents between the ages of 12 and 16 years ($P < .001$).

These values in all the children and adolescents as a group were significantly higher than that of 29 ± 2 pg/mL[4,5] found in adults by using the same assay method ($P < .005$) (Fig 2). In addition, the value in all children was significantly higher ($P < .001$) than that reported in 28 cord blood samples from term neonates, namely, 21 ± 2 pg/mL.[6] Nonetheless, our values and those reported by Scriver et al[9] are not significantly different. Finally, the values found in children aged 11 years or less were not statistically different from the values found in adults by Eisman et al.[4,5] The values found in all children were slightly higher than those reported by Scriver et al[9] of 37 ± 12 pg/mL (mean ± SD), but they studied only 12 normal children in contrast to the 103 healthy children we used to determine the levels during childhood.

1,25-$(OH)_2$D Levels in Childhood Uremia

Nine uremic children, aged 2½ to 13 years, with serum creatinine values between 2.5 and 7.6 mg/dL, had a serum level of 13 ± 5 pg/mL, significantly lower than the value in healthy children ($P < .001$). Seven of these children had tubulointerstitial disease, and two had chronic glomerulonephritis (Table 1). The level found in 11 other children, aged 8 to 16 years, with chronic glomerulonephritis and a serum creatinine concentration between 0.8 to 2.4 mg/dL, was 46 ± 6 pg/dL, significantly higher than the value found in the uremic children ($P < .01$).

The reduction in serum levels of 1,25-$(OH)_2$D was comparable to those reported previously by us in fewer children[10] and in adult uremic subjects.[11,12] The range of values in these nine children was 0 to 39 pg/mL and eight of the values were less than 24 pg/mL (Fig 3). The single patient with a value of 39 pg/mL had posterior urethral valves, a serum creatinine concentration of 2.5 mg/dL, and a serum calcium level of 9.4 mg/dL, and the patient was being treated with 15,000 units of ergocalciferol daily. Nonetheless, this patient had radiologically proved renal osteodystrophy and a serum immunoreactive PTH

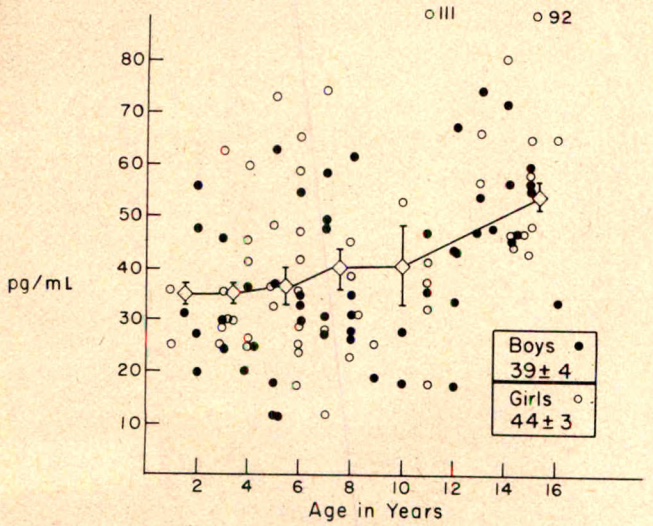

Fig 1.—Levels of 1,25-dihydroxyvitamin D in serum compared with age in children. Man (±SE) values for boys and girls are in inset. Mean (±SE) values (diamonds) are given for patients in varying age ranges. Numbers beside some points indicate serum levels.

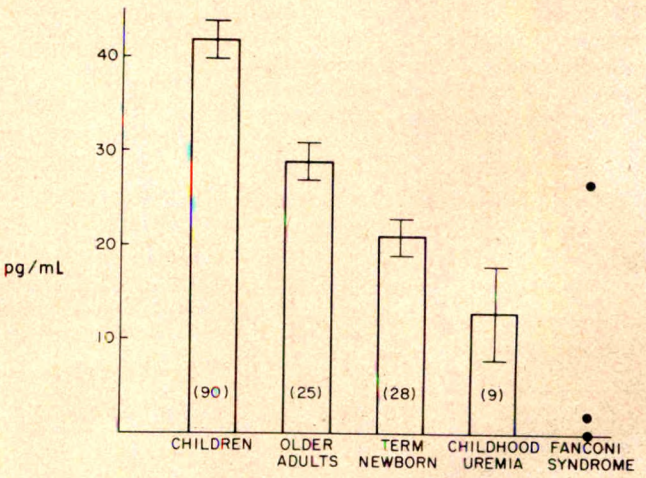

Fig 2.—Mean (±SE) levels of 1,25-dihydroxyvitamin D_3 in sera from various groups. Values for adults more than 25 years old[4,5] and for cord blood from neonates[6] were reported elsewhere. Numbers in parentheses indicate number of patients in each group. Values in healthy children are significantly higher than in other groups.

level of 660 μLEq/mL (normal, < 40 μLEq/mL). After therapy with calcitriol (0.026 μg/kg/24 hr) for five months, the serum level was found to be 78 pg/mL and the immunoreactive PTH level decreased to 230 μLEq/mL. The level of 1,25-$(OH)_2D$ in five patients measured four to six hours after oral therapy with calcitriol (0.015 to .0.050 μg/kg/24 hr) increased to 59 ± 10 pg/mL, a value similar to that of controls (Fig 3).

Levels in Idiopathic Hypoparathyroidism

Thirteen hypocalcemic patients, aged 1 to 14 years, with idiopathic hypoparathyroidism, two of whom had chronic mucocutaneous candidiasis, had a mean value of 16 ± 1 pg/mL, significantly different from control values ($P < .001$) (Table 2). After treatment with calcitriol for several weeks to months in seven patients, a oral dosage of 0.015 to 0.135 μg/kg/24 hr resulted in serum levels of 130 ± 18 pg/mL some four to six hours later and was associated with normocalcemia in six patients. The highest serum value, 295 pg/mL, was found in a previously described patient who had persistent hypocalcemia despite oral dosages of calcitriol of 0.135 μg/kg/24 hr.[13]

Values in Fanconi's Syndrome

The 1,25-$(OH)_2D$ levels in three patients with the typical urinary and bone findings of Fanconi's syndrome are shown (Fig 2). A 5½-year-old boy with nephropathic infantile cystinosis had an undetectable level while receiving 25,000 units of ergocalciferol (vitamin D_2) daily. The blood sample was taken when his serum creatinine concentration was 0.7 mg/dL and his CO_2 combining power was 18 mEq/L. The second patient, aged 14 years, had an autosomal dominant form of Fanconi's syndrome[7]; his serum creatinine level was 6.5 mg/dL and his CO_2 combining power was 18.5 mEq/L. While receiving 1.25 mg of dihydrotachysterol daily, the level of 1,25-$(OH)_2D$ was 2 pg/mL. On the administration of oral calcitriol (0.015 μg/kg/24 hr), the level was found to be 44 pg/mL when measured at both five and 11 months after therapy had begun. Both of these patients had

Table 1.—Clinical Characteristics of Patients With Renal Disease

Patient/ Age, yr	Diagnosis	Height Percentile	Serum Creatinine, mg/dL	Serum 1,25-Dihydroxy-vitamin D, pg/ml
1/11	Infantile polycystic	<3	5.6	19
2/13	Interstitial nephritis	<3	7.6	2
3/2½	Posterior urethral valves	<3	2.5	39
4/12	Congenital hypoplasia	10	5.6	1
5/8	Interstitial nephritis	<3	2.7	0
6/11	Focal sclerosing GN	25	5.9	12
7/13	Membranoproliferative GN	70	3.6	0
8/2	Posterior urethral valves	<3	4.6	23
9/13	Congenital hypoplasia	5	7.5	0
Mean ± SE				13 ± 5
10/14	Chronic proliferative GN	55	1.0	66
11/13	Berger's disease	30	0.9	75
12/8	Minimal lesion nephrotic syndrome	30	0.8	74
13/16	Membranoproliferative GN	75	2.4	30
14/16	Focal sclerosing GN	45	2.0	19
15/13	Focal proliferative GN	75	0.9	19
16/15	Focal proliferative GN	55	1.1	20
17/12	Berger's disease	35	0.8	32
18/13	Focal sclerosing GN	90	1.0	35
19/9	Berger's disease	50	0.8	40
20/14	Familial C4 deficiency	30	1.1	52
Mean ± SE				46 ± 6

*GN indicates glomerulonephritis.

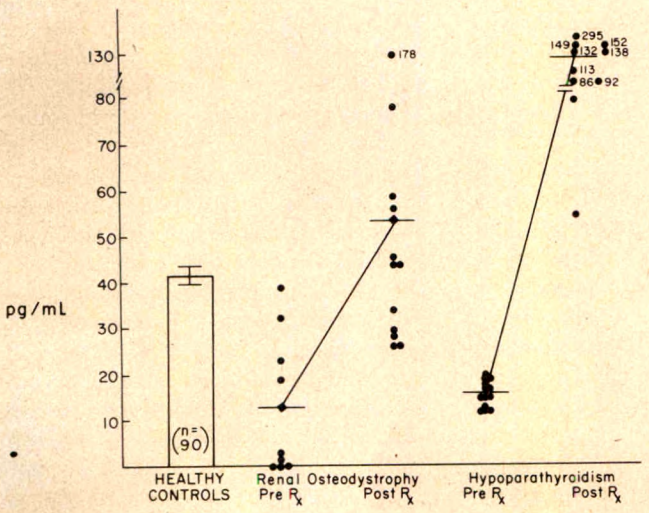

Fig 3.—Serum 1,25-dihydroxyvitamin D_3 levels for healthy children and for uremic and hypoparathyroid children before and after oral calcitriol treatment (R_X). Points indicate individual patients and mean values are shown with bars. Numbers beside some points indicate serum levels. All posttreatment values were obtained several months into therapy and four to six hours after oral dose.

Table 2.—Clinical Characteristics of Patients With Idiopathic Hypoparathyroidism

Patient No./ Age, yr, mo	Clinical Feature	1,25-Dihydroxyvitamin D, pg/mL*
1/1	Isolated idiopathic hypoparathyroidism (IIH)	20
2/4, 9	IIH	19
3/3, 9	IIH	19
4/18	IIH	17
5/16	IIH	17
6/12	IIH	17
7/11	IIH	15
8/10	IIH	13
9/9, 8	IIH	12
10/7, 6	IIH	12
11/3, 3	IIH	16
12/5, 2	Mucocutaneous candidiasis	17
13/14	Mucocutaneous candidiasis	16

*Mean ± SE, 16 ± 1 pg/mL.

clinical and radiologic evidence of rickets prior to treatment with calcitriol. Serum calcium levels were 9.1 and 8.4 mg/dL, respectively, when the initial 1,25-$(OH)_2$D levels were determined.

A third patient, aged 15 years, had the typical features of Lowe's syndrome and a serum 1,25-$(OH)_2$D level of 29 pg/mL while receiving 50,000 units of ergocalciferol. This patient did not have rickets but did have osteoporosis. The serum CO_2 combining power was 23 mEq/L. This patient had a 1,25-$(OH)_2$D level well below the value of 55 ± 2 pg/mL (mean ± SE) found in 29 adolescents aged 12 to 16 years.

COMMENT

The finding of higher levels of 1,25-$(OH)_2$D in children between the ages of 1 and 16 years than in adults[4,5,14,15] or in cord blood[6] suggests that the concentrations of this active vitamin D metabolite reach a peak during childhood. The level found by Eisman et al[4,5] in normal adults was 29 ± 2 pg/mL, comparable to the values of 33 ± 6 pg/mL found by Haussler et al.[11,12] Of interest, these levels seem to be the highest during adolescence, a period of rapid growth and bone mineral accretion. Estrogen is known to augment 1α-hydroxylase activity and pregnancy can elevate 1,25-$(OH)_2$D levels.[16,17] Possibly, the increased values of 1,25-$(OH)_2$D are related to hormonal changes taking place during puberty and permit the greater intestinal mineral absorption needed for growth. Unfortunately, we have not established the normal levels for the first 12 months of life, the period of most rapid growth during life. Investigators using 1,25-$(OH)_2$D levels in adolescents should be aware of the higher levels in this age group.

It is of interest that the 1,25-$(OH)_2$D concentrations found in children in an urban environment with reduced sunlight exposure (New York City) are similar to those in children living in a rural setting (Wisconsin). The values were also similar regardless of the patient's sex or the season. The values in adolescents were higher in both locations. The value for 1,25-$(OH)_2$D in sera is approximately 0.1% to 0.2% of that reported for 25-hydroxyvitamin D (25-OH-D) and 1% of that for 24,25-dihydroxyvitamin D (24,25-$(OH)_2$D),[18] indicating the relative ratio of these respective compounds in children is 1000:100:1.

Uremia is known to impair the production of 1,25-$(OH)_2$D in man,[19] and the serum levels in uremic adults are low.[4,5,11,12] These patients, undergoing long-term hemodialysis, were anephric and had undetectable levels of 1,25-$(OH)_2$D. Our patients are children, totally ambulatory, whose conditions are managed by conventional therapy for chronic renal insufficiency, and they have an average serum creatinine clearance of 5.4 mg/dL. Nonetheless, the levels were substantially reduced in these nine children and were found to be in the normal range in the five patients sampled six hours after treatment with 0.015 to 0.05 μg/kg/24 hr of calcitriol.

Patients with hypoparathyroidism have absent or reduced levels of PTH and elevated serum (and intracellular) levels of phosphate. A reduction in circulating 1,25-$(OH)_2$D would be anticipated.[1] Accordingly, as reported by Rosen et al[8] and Kooh et al,[20] the levels of this metabolite are low. We find a reduction of similar extent to that found in uremia. However, in contrast to the situation in uremia, the serum levels increased from a mean of 16 to 130 pg/mL six hours after a roughly comparable oral dose. Rosen et al[8] further demonstrated that these values return to pretreatment levels after 24 hours. Whether there are differences in the pharmacokinetics of 1,25-$(OH)_2$D in patients with uremia vs patients with hypoparathyroidism remains unknown. Despite levels that were three times normal, these seven patients were not hypercalcemic. Indeed, one patient, previously reported by us[13] remained hypocalcemic in the face of high levels (295 pg/mL) after therapy with high doses of calcitriol (0.135 μg/kg/24 hr). Of interest is that our posttreatment values were higher than those reported in two patients with pseudohypoparathyroidism who had overt hypercalcemia at serum 1,25-$(OH)_2$D levels of 53 and 77 pg/mL.[21] These latter values were determined by using a different bioassay and, therefore, may not be entirely comparable.

The levels in three patients with Fanconi's syndrome were low, similar to those reported by Brewer et al[22] who studied the metabolites in plasma after 25-OH-[^{3}H]D administration. Although it is well recognized that hypophosphatemia resulting from reduced renal tubular phosphate reabsorption is important in the pathogenesis of bone disease, healing of rickets in Fanconi's syndrome can occur with large doses of vitamin D or with intensive alkali therapy.[23] Recent animal studies have suggested that systemic metabolic acidosis per se

impairs the conversion of 25-OH-D to 1,25-$(OH)_2$D.[14,15,24,25] Using the maleic acid model of Fanconi's syndrome, which results in systemic acidosis, the activity of 25-OH-D_3-1α-hydroxylase in rats was reduced despite a normal glomerular filtration rate.[15] Our two patients with subnormal serum CO_2 combining power values had extremely low 1,25-$(OH)_2$D levels, although one of these patients had renal insufficiency when the sample was obtained. The child with Lowe's syndrome had a level more than 2 SD below the value of 54 ± 11 pg/mL (mean ± SD) found in healthy 13- to 16-year olds. Further values from patients with Fanconi's syndrome would obviously be of interest.

This study demonstrates that the circulating levels of 1,25-$(OH)_2$D are higher in older than in younger children and further demonstrates that children with uremia, hypoparathyroidism, and Fanconi's syndrome have reduced serum levels of this active metabolite.

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Nonproprietary Name and Trademark of Drug

Calcitriol—*Rocaltrol.*

References

1. DeLuca HF: Recent advances in our understanding of the vitamin D endocrine system. *J Lab Clin Med* 82:7-26, 1976.

2. Raisz LG, Trummel CL, Holick MF, et al: 1,25-Dihydroxycholecalciferol: A potent stimulator of bone resorption in tissue culture. *Science* 175:768-769, 1972.

3. Fomon SE: *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974, pp 292-293.

4. Eisman JA, Hamstra AJ, Kream BE, et al: 1,25-Dihydroxyvitamin D in biological fluids: A simplified and sensitive assay. *Science* 193:1021-1023, 1976.

5. Eisman JA, Hamstra AJ, Kream BE, et al: A sensitive, precise, and convenient method for determination of 1,25-dihydroxyvitamin D in human plasma. *Arch Biochem Biophys* 176:235-243, 1976.

6. Steichen JJ, Tsang RC, Gratton TL, et al: Postnatal changes in vitamin D metabolites in relationship to parathyroid hormone (PTH) and ionized Ca (iCa), abstracted. *J Pediatr* 93:309, 1978.

7. Friedman AL, Trygstad CW, Chesney RW: Autosomal dominant idiopathic Fanconi syndrome with early renal failure. *Am J Med Genet* 2:225-232, 1978.

8. Rosen JF, Fleischman AR, Finberg L, et al: 1,25-Dihydroxycholecalciferol: Its use in the long-term management of idiopathic hypoparathyroidism in children. *J Clin Endocrinol Metab* 45:457-468, 1977.

9. Scriver CR, Reade TM, DeLuca HF, et al: Serum 1,25-dihydroxyvitamin D levels in normal subjects and in patients with hereditary rickets or bone disease. *N Engl J Med* 299:976-979, 1978.

10. Chesney RW, Moorthy AV, Eisman JA, et al: Increased growth after long-term oral 1α,25-dihydroxyvitamin D_3 in childhood renal osteodystrophy. *N Engl J Med* 298:238-242, 1978.

11. Haussler MR, Baylink DJ, Hughes MR, et al: The assay of 1α,25-dihydroxyvitamin D_3: Physiologic and pathologic modulation of circulating hormone levels. *Clin Endocrinol* 5(supp):151S-165S, 1976.

12. Haussler MR, Hughes MR, Pike JW, et al: Radioligand and receptor assay for 1,25-dihydroxyvitamin D: Biochemical, physiologic and clinical applications, in Norman AW, Schaefer K, Coburn JW, et al (eds): *Vitamin D: Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism.* Berlin, Walter de Gruyter, 1977, pp 473-482.

13. Chesney RW, Horowitz SD, Kream BE, et al: Failure of conventional doses of 1α,25-dihydroxycholecalciferol to correct hypocalcemia in a girl with idiopathic hypoparathyroidism. *N Engl J Med* 297:1272-1275, 1977.

14. Sauveur B, Garabedian M, Fellot C, et al: The effect of induced metabolic acidosis on vitamin D_3 metabolism in rachitic chicks. *Calcif Tissue Res* 23:121-124, 1977.

15. Brewer ED, Tsai HC, Szeto KS, et al: Maleic acid-induced impaired conversion of 25(OH)D_3 to 1,25$(OH)_2D_3$: Implications for Fanconi's syndrome. *Kidney Int* 12:244-252, 1977.

16. Tanaka Y, Castillo L, DeLuca HF: Control of renal vitamin D hydroxylases in birds by sex hormones. *Proc Natl Acad Sci USA* 73:2701-2705, 1976.

17. Pike JW, Toverud S, Boass A, et al: Circulating 1α,25-$(OH)_2$D during physiological states of calcium stress, in Norman AW, Schaefer K, Coburn J, et al (eds): *Vitamin D: Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism.* Berlin, Walter de Gruyter, 1977, pp 187-189.

18. Weisman Y, Reiter E, Root A: Measurement of 24,25-dihydroxyvitamin D in sera of neonates and children. *J Pediatr* 91:904-908, 1977.

19. Mawer EB, Taylor CM, Backhouse J, et al: Failure of formation of 1,25-dihydroxycholecalciferol in chronic renal insufficiency. *Lancet* 1:626-628, 1973.

20. Kooh SW, Fraser D, DeLuca HF, et al: Treatment of hypoparathyroidism and pseudohypoparathyroidism with metabolites of vitamin D: Evidence of impaired conversion of 25-hydroxyvitamin D to 1α,25-dihydroxyvitamin D. *N Engl J Med* 293:840-844, 1975.

21. Bell NH, Stern PH: Hypercalcemia and increases in serum hormone value during prolonged administration of 1α,25-dihydroxyvitamin D. *N Engl J Med* 298:1241-1243, 1978.

22. Brewer E, Tsai HC, Morris RC Jr: Metabolism of 25-hydroxyvitamin D_3 (25-OH-D_3) in children with Fanconi's syndrome, abstracted. *Am Soc Nephrol*, November 1975, p 1.

23. Root AW, Harrison HE: Recent advances in calcium metabolism: II. Disorders of calcium homeostasis. *J Pediatr* 88:177-199, 1976.

24. Lee SW, Russell J, Avioli LV: 25-Hydroxycholecalciferol to 1,25-dihydroxycholecalciferol: Conversion impaired by systemic metabolic acidosis. *Science* 195:994-996, 1977.

25. Booth BE, Tsai HC, Morris RC: Metabolic acidosis in the vitamin D-deficient chick. *Metabolism* 26:1099-1105, 1977.

Supranormal 25-Hydroxyvitamin D and Subnormal 1,25-Dihydroxyvitamin D

Their Role in X-linked Hypophosphatemic Rickets

Russell W. Chesney, MD; Richard B. Mazess, PhD; Philip Rose; Alan J. Hamstra, MS; Hector F. DeLuca, PhD

• **Serum 25-hydroxyvitamin D (25-OH-D) and 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$) and bone mineral content by the photon-absorption technique were determined in eight patients with X-linked hypophosphatemic rickets treated for at least 24 months with oral sodium phosphate and high-dosage ergocalciferol (vitamin D_2). Mean 25-OH-D_2 level was 129.5 ± 67.5 ng/mL (mean ± SD); the level of 25-OH-D_3 was 10.5 ± 5.8 ng/mL. These values were significantly higher than in normal subjects (total 25-OH-D mean of 27 ± 10 ng/mL). Serum 1,25-$(OH)_2D$ was 16.9 ± 8.5 pg/mL (mean ± SD) in the eight patients, significantly lower than 47 ± 16 pg/mL in 27 age-matched controls. Values indicative of significant demineralization were found in seven of the eight phosphate-treated patients, who had no radiologic evidence of rickets. These results suggest that any theory of the pathogenesis of this disorder must account for inappropriate renal vitamin D metabolism and for renal hyperphosphaturia. The failure of high-dosage oral phosphate and ergocalciferol to fully correct demineralization may suggest a role for calcitriol (1,25-$(OH)_2D_3$) as a therapeutic agent.**

(*Am J Dis Child* 134:140-143, 1980)

X-linked hypophosphatemic rickets is characterized by hyperphosphaturia despite severe hypophosphatemia, by normocalcemia, and by rickets unresponsive to therapy with doses of vitamin D that cure simple vitamin D deficiency. This condition, therefore, has sometimes been called vitamin D-resistant rickets.[1] The net tubular reabsorption of phosphate is decreased in all patients with this disorder.[2] Two completely opposing theories of the pathogenesis of this disorder have emerged since the first clinical description in 1937 by Albright et al.[3] Albright and co-workers ascribed the disorder to an abnormality of vitamin D metabolism that would result in intestinal calcium malabsorption, secondary hyperparathyroidism with hyperphosphaturia, and hypophosphatemia. However, the finding of normal or only slightly elevated plasma immunoreactive parathyroid hormone (iPTH) levels in untreated patients with this disorder[4,5] led to support for a second pathogenic mechanism. In this second hypothesis, hypophosphatemia was directly related to defective transport of the phosphate ion across the renal tubule and intestinal mucosa. This was viewed as an isolated transport defect that ultimately resulted in undermineralization of bone and in rickets.[6]

See p 135.

The original hypothesis required the existence of abnormalities of vitamin D metabolism to account for the intestinal calcium and phosphate malabsorption found in patients with this disorder.[7] However, the levels of 25-hydroxyvitamin D (25-OH-D) have been found to be normal in at least two separate studies.[8,9] Recently, Drezner and Haussler[10] have reported that the circulating levels of 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$), the most active metabolite of vitamin D described to date, are normal in patients with this disorder. Nonetheless, these authors point out that a normal level is somewhat surprising since these patients are hypophosphatemic and presumably have reduced

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renal tubular intracellular phosphate levels, a known stimulus to 1,25-$(OH)_2D$ production.[11] In contrast, Scriver et al[12] have recently reported that serum 1,25-$(OH)_2D$ levels were significantly subnormal in patients with hypophosphatemic rickets. Using a precise assay of 1,25-$(OH)_2D$, we have also examined the levels of this metabolite in eight patients with hypophosphatemic rickets.

Radiologic evidence of healing of rickets and improved growth velocity have been reported after the administration of several grams of oral phosphate given every four to five hours in addition to high-dose vitamin D (20 to 75×10^3 units per day).[13-15] Histologic evaluation of bone after this form of therapy has not been extensively reported, and it is not established that the therapeutic regimen of phosphate and high-dose vitamin D completely corrects the bone disease. Recently, Glorieux et al[16] have reported persistence of osteomalacia and widened osteoid seams in bone biopsy specimens from patients treated with ergocalciferol (vitamin D_2) and phosphate. Accordingly, we[17] have examined the bone mineral content (BMC) of our patients, whose conditions were treated with this therapeutic regimen, using the technique of direct photon absorptiometry and have compared these results with appropriate control values.

PATIENTS AND METHODS

The eight children (six girls and two boys), aged 2 to 13 years, had short stature (a height less than the third percentile), hypophosphatemia (<2.5 mg/dL), and radiologic evidence of rickets prior to treatment. A family history of hypophosphatemic rickets was found in five children, two of whom were siblings; and in each instance, the history was consistent with an X-linked inheritance pattern. The mothers of two other patients had fasting hypophosphatemia, 2.4 mg/dL and 2.3 mg/dL, respectively, but they were not short or bowed. The other child could be considered to have the sporadic form of the disease. None had aminoaciduria, glucosuria, or renal bicarbonate wasting. None of the patients had associated myopathy, and in each case, rickets was radiologically verified as improved after therapy. Prior to therapy, the serum iPTH level was in the normal range (less than 40 μLEq/mL).

Treatment consisted of oral sodium phosphate (Joulie's solution) given at 1.5 to 3.6 g daily in five divided doses[15] and ergocalciferol given at 20,000 to 75,000 units daily (0.5 to 1.875 mg). Each patient had been treated for at least 24 months with this regimen, with a resultant increase in height from less than the third percentile to between the tenth and 25th percentiles using growth standards of the National Center for Health Statistics.

Blood was obtained for vitamin D assay from control subjects who were undergoing elective surgery, including tonsillectomy, herniorrhaphy, or strabismus repair. Serum samples were obtained from these healthy children at different times during the year. Informed consent was obtained from the parents of these normal subjects according to a protocol approved by the Human Subjects Committee of the University of Wisconsin Center for Health Sciences, Madison.

Vitamin D metabolites were measured using specific binding assays after extraction of serum samples in methanol and methylene chloride and separation by fractionating column (Sephadex LH-20) chromatography. The vitamin D metabolites, 25-OH-D_2, 25-OH-D_3, 1,25-$(OH)_2D_2$ and 1,25-$(OH)_2D_3$ were separated by high-pressure liquid chromatography as described by Eisman et al.[18-20] The 25-hydroxymetabolites were measured by direct high-pressure liquid chromatography, and the 1,25-dihydroxyvitamin D levels were measured using the vitamin D-deficient chick intestinal cytosol protein.[18-20]

Absorptiometric determinations of BMC were measured by the use of a narrow beam of low-energy radiation from a monoenergetic radionuclide source (iodine 125 at 27.4 kiloelectron volts). The source and photon detector were moved across the radius and ulna of the nondominant arm as we have described elsewhere.[17,21] Changes in beam intensity are coupled to attenuation by bone mineral and the integrated attenuation pattern is proportional to the mass of mineral in the scan path. The BMC, bone width (BW) (proportional to the length of the scan path), and their ratio (BMC/BW) were ascertained in both forearm bones at a point one third of the forearm length proximal to the ulnar styloid. The radiation dose was less than 10 mrem (compared with the International Commission on Radiological Units maximal limb dose of 7,500 mrem). The precision of this method is within 2% to 3%, and these scans accurately indicate the ash weight of bone to within 1% to 3%.[22] The BMC, BW, and BMC/BW values obtained were compared with values obtained from more than 800 healthy age- and sex-matched controls, reported elsewhere.[17] Multiple regressions were calculated in each sex for the BMC of each bone using height, weight, age, and BW as independent variables. The SE of estimate was about 10%, so that a reduction of more than 20% in BMC or BMC/BW ratio indicated significant demineralization (or a change of >2SD).[17,21]

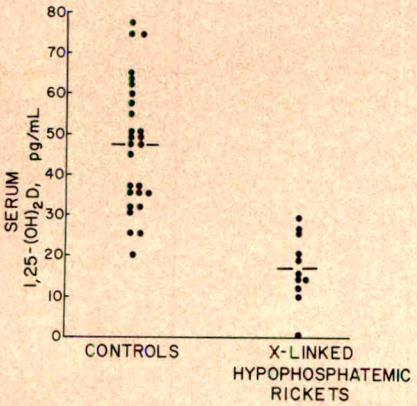
Serum iPTH was assayed as described elsewhere.[4] Statistical analysis was done by Student's t test.

RESULTS

Serum was obtained from patients three to four hours after their early morning dose of oral phosphate and ergocalciferol for the following values: serum calcium, magnesium, phosphorus, alkaline phosphatase activity, vitamin D metabolite levels, and iPTH levels. Simultaneous roentgenograms of knees and hands and photon absorptiometric measurements were also obtained. Height was measured using a fixed wall stadiometer.

Serum calcium was 9.42 ± 0.26 mg/dL (mean ± SD) in 11 measurements from the eight patients (normal range for our laboratory, 9.5 to 10.4 mg/dL). The serum phosphate concentration was 3.04 ± 0.46 mg/dL, in comparison with the normal range for children of this age of 3.5 to 5.8 mg/dL. The serum alkaline phosphatase value was 378 ± 217 IU/L, the normal in our laboratory being 280 IU/L or less. Serum magnesium value was normal. No rickets was observed. However, coarsened trabeculations and radiologic evidence of incomplete healing of rickets were noted in the two sisters; whereas other laboratory studies, including serum phosphorus levels of 2.8 mg/dL and 2.7 mg/dL, respectively, and alkaline phosphatase values of 756 IU/L and 864 IU/L, indicated poor compliance with the treatment regimen. These girls also had severe bowing of their legs.

Serum levels of iPTH were measured in five patients while receiving oral phosphate and ergocalciferol. Prior to receiving this therapeutic regimen, the serum iPTH levels were in the normal range (<40 μL Eq/mL) for each patient. The mean level for the five patients receiving therapy was 61.1 ± 13.9 μL Eq/mL, indicative of mild hyperparathyroidism.



Concentration of $1,25\text{-}(OH)_2D$ in serum. Concentration was measured in serum from 27 healthy, age-matched control subjects and from eight patients with hypophosphatemic rickets. Means in control subjects, 47 ± 16 pg/mL, and in patients, 16.9 ± 8.5 pg/mL, were significantly different from one another ($P < .001$).

The serum levels of 25-OH-D metabolites were substantially elevated, particularly 25-OH-D_2. The serum 25-OH-D_2 level was 129.5 ± 67.5 ng/mL (mean ± SD) and the 25-OH-D_3 level was 10.5 ± 5.8 ng/mL. The total 25-OH-D_2 and 25-OH-D_3 level of 140 ± 66 ng/mL ($n = 11$) was significantly higher than the value in 30 controls of 27 ± 10 ng/mL ($P < .001$). The combined, simultaneous levels of $1,25\text{-}(OH)_2D_2$ and $1,25\text{-}(OH)_2D_3$ are shown in the Figure in comparison with the levels of age-matched control subjects. The mean level of $1,25\text{-}(OH)_2D$ in the eight patients was 16.9 ± 8.5 pg/mL, significantly lower than the level in 27 healthy children of 47 ± 16 pg/mL (mean ± SD), $P < .001$. The values for controls shown in the Figure represent the values found in healthy children of the same age in years as the patients.

Nine measurements of photon absorptiometry were available when vitamin D metabolites were also obtained. Values indicative of significant demineralization (>−2SDs) using the BMC/BW ratio were found in seven of the eight patients; each of the same seven patients was demineralized when the BMC of either the radius or the ulna was examined. These hypophosphatemic patients had a reduction in BMC of minus 2 to 2.5SD in comparison with values of minus 3 to 4 SD found by us[17] in uremic subjects. Furthermore, the greatest reduction in BMC and BMC/BW ratio was found in the two children with poor treatment compliance.

COMMENT

In these patients with the typical features of X-linked hypophosphatemic rickets undergoing treatment with oral phosphate and high doses of ergocalciferol, the serum levels of 25-OH-D were greatly elevated, being as high as ten times normal. Nonetheless, there was evidence of a reduction in the conversion of 25-OH-D to $1,25\text{-}(OH)_2D$ in these patients since $1,25\text{-}(OH)_2D$ levels were substantially reduced. The concentrations of $1,25\text{-}(OH)_2D$ found in our patients were similar to those found by Scriver et al[12] using the same competitive binding assay in 14 patients. These authors found reduced levels in both treated and untreated patients. Therefore, the levels seem to be reduced in at least 22 different children with this disorder. Of importance is that these data come from two separate parts of North America, Wisconsin and Quebec, and thus indicate the same finding in different regions. The reports by Drezner and Haussler et al[10,23] of normal values of $1,25\text{-}(OH)_2D$ in hypophosphatemic patients is somewhat at variance with these results. Drezner and Haussler have reported values of 30 ± 8.4 pg/mL in ten patients aged 13 to 35 years. In addition, their patients were not treated with vitamin D or phosphate. They postulated that such therapy could have led to a reduction in circulating $1,25\text{-}(OH)_2D$ concentrations by inhibiting the activity of the 1α-hydroxylase enzyme. Nonetheless, from our own data for healthy normal subjects of ages 13 to 35 years (during adolescence and the young adult period), the mean plasma level of $1,25\text{-}(OH)_2D$ should be 50 ± 10 pg/mL. Accordingly, a serum level of 30 pg/mL is low for patients in this age group. The normal values given by Haussler et al,[23] 20 to 45 pg/mL, may not be from subjects of a comparable age.

Drezner and Haussler[10] have also made the point that normal plasma $1,25\text{-}(OH)_2D$ levels would be low in the face of severe hypophosphatemia. Indeed, these values should probably be elevated since a reduced intracellular phosphate level leads to increased $1,25\text{-}(OH)_2D$ synthesis.[11] It is of interest that our patients, with a mean serum phosphorus value of 3.04 ± 0.47 mg/dL, well below the normal range for age, have demonstrated reduced $1,25\text{-}(OH)_2D$ levels. However, the $1,25\text{-}(OH)_2D$ levels were obtained three to four hours after phosphate therapy, when phosphate levels are known to have decreased from the peak found after one to two hours.[15] It is thus difficult to fully know from the data at hand whether or not renal 1α-hydroxylase response is appropriate in treated patients with fluctuating serum phosphate concentrations. Nonetheless, the finding of Scriver et al[12] that both treated and untreated hypophosphatemic patients have reduced $1,25\text{-}(OH)_2D$ levels points to impaired 1α-hydroxylase activity at a variety of serum phosphate levels.

The level of serum calcium in our patients may have been low enough to cause elevated serum iPTH levels, another potent stimulus to the production of $1,25\text{-}(OH)_2D$.[24] We have measured iPTH values in five of these patients after the onset of therapy and have found that these values were about 50% higher than normal, probably related to the high oral phosphate intake.[15] Therefore, reduced $1,25\text{-}(OH)_2D$ levels found in these patients were present despite hypophosphatemia and elevated iPTH levels, known stimuli to $1,25\text{-}(OH)_2D$ synthesis.

The differences in $1,25\text{-}(OH)_2D$ levels reported to date may also reflect different patient groups with this disorder since it is recognized that this is a clinically heterogenous disorder.[1,3,12] Some patients have bone disease without overt rickets,[12] some have parathyroid adenomas,[3] and the genetics of this condition may be quite varied.[1,13] Within a given clinical subset of hypophosphatemic rickets, forms with varying vitamin D metabolite levels may prevail.

We have used the photon absorptiometric technique to demonstrate

that therapy with oral phosphate and high-dose ergocalciferol may not fully correct undermineralization of bone. Histologic evidence suggests that this form of treatment may not fully correct the osteoidosis of hypophosphatemia.[16,25] Our data would indicate that substantial demineralization is present after phosphate supplementation and thus supports the histologic data. This finding of demineralization after phosphate and ergocalciferol therapy could indicate that suboptimal levels of these two agents were used in treating these patients. However, serum phosphate levels were generally maintained at more than 3.5 mg/dL, and serum iPTH levels were elevated in five of the patients, indicative of excessive oral phosphate intake. In addition, Glorieux et al[25] have shown evidence of osteomalacia and widened osteoid seams using the same treatment regimen. Whether oral 1,25-$(OH)_2D$ treatment will correct this undermineralization, as has been suggested in a few patients,[25-27] awaits long-term critical evaluation. Certainly, our findings of reduced 1,25-$(OH)_2D$ levels suggests that trials of long-term replacement therapy with this vitamin D analog should be undertaken.

The finding of reduced 1,25-$(OH)_2D$ levels in patients with hypophosphatemic rickets is unexpected according to the two major pathogenetic theories about this condition. Albright's hypothesis states that hypophosphatemia follows secondary hyperparathyroidism.[1-3] The other hypothesis states that an isolated renal phosphate leak is primary.[2,6] In either instance, elevated 1,25-$(OH)_2D$ levels would be anticipated. Rasmussen and Anast[1] have recently postulated that a defect in the distal tubule could account for both the renal phosphate leak and the block in 1,25-$(OH)_2D$ synthesis, and in their hypothetical models, the renal tubule is supersensitive to the action of PTH as well. Our data would indicate that any theory of the pathogenesis of this disorder must account for hypophosphatemia with a renal phosphate leak and reduced 1,25-$(OH)_2D$ levels.

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Nonproprietary Name and Trademark of Drug

Calcitriol—*Rocaltrol.*

References

1. Rasmussen H, Anast C: Familial hypophosphatemic (vitamin D-resistant) rickets and vitamin D-dependent rickets, in Stanbury JB, Wyngaarden JB, Fredrickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 4. New York, McGraw-Hill Book Co, 1978, pp 1537-1562.

2. Scriver CR: Rickets and the pathogenesis of impaired tubular transport of phosphate and other solutes. *Am J Med* 57:43-49, 1974.

3. Albright F, Butler AM, Bloomberg E: Rickets resistant to vitamin D therapy. *Am J Dis Child* 54:529-547, 1937.

4. Arnaud C, Glorieux F, Scriver CR: Serum parathyroid hormone in X-linked hypophosphatemia. *Science* 173:845-847, 1971.

5. Lewy JE, Cabana EC, Repetto HA, et al: Serum parathyroid hormone in hypophosphatemic vitamin D-resistant rickets. *J Pediatr* 81:294-300, 1972.

6. Fraser D, Scriver CR: Familial forms of vitamin D-resistant rickets revisited: X-linked hypophosphatemia and autosomal recessive vitamin D dependency. *Am J Clin Nutr* 29:1315-1329, 1976.

7. Walton J: Familial hypophosphatemic rickets: A delineation of its subdivisions and pathogenesis. *Clinical Pediatr* 15:1007-1012, 1976.

8. Balsan S, Garabedian M: 25-Hydroxycholecalciferol: A comparative study in deficiency rickets and different types of resistant rickets. *J Clin Invest* 51:749-759, 1972.

9. Haddad JG Jr, Chyu KJ, Hahn TJ, et al: Serum concentrations of 25-hydroxyvitamin D in sex-linked hypophosphatemic vitamin D-resistant rickets. *J Lab Clin Med* 81:22-27, 1973.

10. Drezner MK, Haussler MR: Serum 1,25-dihydroxyvitamin D in bone disease. *N Engl J Med* 300:435-436, 1979.

11. DeLuca HF: Recent advances in our understanding of the vitamin D endocrine system. *J Lab Clin Med* 87:7-26, 1976.

12. Scriver CR, Reade TM, DeLuca HF, et al: Serum 1,25-dihydroxyvitamin D levels in normal subjects and in patients with hereditary rickets or bone disease. *N Engl J Med* 299:976-979, 1978.

13. Harrison HF, Harrison HC, Lifshitz F, et al: Growth disturbance in hereditary hypophosphatemia. *Am J Dis Child* 112:290-297, 1966.

14. McEnery PT, Silverman FN, West CD: Acceleration of growth with combined vitamin D-phosphate therapy of hypophosphatemic resistant rickets. *J Pediatr* 80:763-774, 1972.

15. Glorieux FH, Scriver CR, Reade TM, et al: Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. *N Engl J Med* 287:481-487, 1972.

16. Glorieux FH, Bordier PJ, Marie P, et al: Inadequate bone response to phosphate and vitamin D in familial hypophosphatemic rickets (FHR), in Massry SG, Ritz E, Rapado A (eds): *Homeostasis of Phosphate and Other Minerals*. New York, Plenum Publishing Corp, 1978, pp 227-232.

17. Chesney RW, Mazess RB, Rose P, et al: Bone mineral status measured by direct photon absorptiometry in childhood renal disease. *Pediatrics* 60:864-872, 1977.

18. Eisman JA, Shepard RM, DeLuca HF: Determination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 in human plasma using high-pressure liquid chromatography. *Anal Biochem* 80:298-305, 1977.

19. Eisman JA, Hamstra AJ, Kream BE, et al: A sensitive, precise and convenient method for the determination of 1,25-dihydroxyvitamin D in human plasma. *Arch Biochem Biophys* 176:235-243, 1976.

20. Horst RL, Shepard RM, Jorgensen NA, et al: The determination of 24,25-dihydroxyvitamin D and 25,26-dihydroxyvitamin D in plasma from normal and nephrectomized man. *J Lab Clin Med* 93:277-285, 1979.

21. Chesney RW, Mazess RB, Rose P, et al: Effect of prednisone on growth and bone mineral content in childhood glomerular disease. *Am J Dis Child* 132:768-772, 1978.

22. Mazess RB: Estimation of bone and skeletal weight by direct photon absorptiometry. *Invest Radiol* 6:52-60, 1971.

23. Haussler MR, Hughes M, Baylink D, et al: Influence of phosphate depletion on the biosynthesis and circulating level of 1α,25-dihydroxyvitamin D. *Adv Exp Med Biol* 81:233-250, 1977.

24. Hughes MR, Brumbaugh PF, Haussler MR, et al: Regulation of serum 1α,25-dihydroxyvitamin D_3 by calcium and phosphate in the rat. *Science* 190:579-580, 1975.

25. Glorieux FH, Bordier PJ, Marie P, et al: The response of bone to oral phosphate salts (Pi), ergocalciferol (D_2) and/or 1,25-dihydroxycholecalciferol (1,25-DHCC) in familial hypophosphatemia. Read before the Fourth Workshop on Vitamin D, Berlin, Feb 21, 1979, p 296A.

26. Hirschman GH, DeLuca HF, Chan JCM: Hypophosphatemic vitamin D-resistant rickets: Metabolic balance studies in a child receiving 1,25-dihydroxyvitamin D_3, phosphate and ascorbic acid. *Pediatrics* 61:451-457, 1978.

27. Drezner MK, Lyles KW, Haussler MR, et al: Abnormal homeostatic regulation of 1,25-dihydroxycholecalciferol biosynthesis: A factor in the genesis of X-linked hypophosphatemic rickets. Read before the Fourth Workshop on Vitamin D, Berlin, Feb 21, 1979, p 299A.

Laryngeal Mucous Gland Excess in Victims of Sudden Infant Death

B. Raymond Fink, MD, J. Bruce Beckwith, MD

• **Larynges from 13 victims of sudden infant death syndrome (SIDS) and from ten controls of comparable age were subjected to serial histological transverse section and examined for structural differences that bear on functional performance. The cross-sectional area of mucous glands in the vestibular fold, expressed as a percent of the total cross-sectional area of the fold was 19.52 ± 8.56 (mean ± SD in the SIDS specimens), and 12.56 ± 6.25 in the controls. The difference is statistically significant and suggests that excess mucous laryngeal secretion may be present in at least some cases of the syndrome.**

(*Am J Dis Child* 134:144-146, 1980)

The term sudden infant death syndrome (SIDS) is conventionally applied to a sudden and unexpected death in which a thorough postmortem examination fails to demonstrate inherently lethal pathology.[1] In recent years, at least one investigator has reported finding certain lesions, including thickened pulmonary vessel walls, that he attributes to chronic hypoxemia[2]; the small pulmonary arteries of cases of SIDS may have 1.6 times as much muscle as those of controls.[3] Some other observers, however, have been unable to confirm the findings.[4] A cause of recurrent hypoxemia is available in the long periods of apnea observed with quiet sleep (NREM sleep) in infants,[5] and such apnea episodes have been held responsible for "near misses."[6]

A history and signs of upper respiratory infection are common in SIDS victims, but are usually too mild to be the direct cause of death. However, Guilleminault et al[6] have shown that upper airway apnea occurs more frequently than usual in infants with such infections, and believe that this may trigger a fatal cardiac arrhythmia during a period of NREM sleep.

The results of a recent study in this laboratory stressed the importance of elastic elements in the reopening of the closed larynx[7] and led us to survey the histology of larynges from SIDS and non-SIDS deaths. In the course of examination of histological sections treated with elastic tissue stains, an apparent divergence was noted in the morphology of the mucous glandular tissue in the vestibular folds of the two groups. A morphometric sampling of this tissue was therefore undertaken and the results are as follow.

MATERIAL AND METHODS

The material consisted of the larynges from 13 victims of SIDS and ten infants who died from other causes and who served as controls. In each instance, permission to remove the larynx for study was obtained individually from the parents. Owing to the scarcity of control specimens in comparison to SIDS specimens, the SIDS larynges subjected to study were selected to compare as closely as possible with the ages of the controls. The selection was made prior to the histological examination of the specimens.

The complete larynx was fixed in 4% formaldehyde and embedded in paraffin. Serial transverse sections 10 μ thick were cut from the tissue between the top of the vestibular folds and the laryngeal sinus. Two sections, one from the craniad and one from the caudad region of the left vestibular fold, respectively at the minimum and maximum anteroposterior lengths of the saccule, were selected in each larynx, with the exception of specimen 75-11, for which tissue from only the caudad level was available and the sections came from the top and bottom of this piece. The selections were made by a technical assistant unaware of the nature of the survey, before staining with hematoxylin-eosin. Thus, the sections examined represent an unbiased selection of samples from each specimen. The sections were then coded by another assistant so that their source (SIDS or control) was unknown to the observer (B.R.F.). The entire set of 45 slides was assembled before measurements began.

The sections were examined in a binocular microscope at ×25 magnification. The cross-sectional area of the vestibular fold and of the mucous glands in the fold was measured with a micrometer grating subdivided into 100 squares of 0.01 sq mm, inserted in the left ocular. Grid squares half filled by mucous gland were counted as 1; squares less than half covered by mucous gland were counted as 0.

All soft tissue in the left vestibular fold, defined as the soft tissue medial to the thyroid cartilage and anterior to a line tangent to the posterior surface of the arytenoid cartilage, was included in the measurement. Each grid was counted twice, first horizontally and then vertically. The measurements agreed within 2% and were averaged.

The ratio of total number of grid squares occupied by mucus or by mucous gland tissue to the total number of grid squares occupied by the vestibular fold was calculated. Lymphoid tissue was excluded from the count of mucous tissue. For convenience, the ratio multiplied by 100 will be referred to as the mucous gland index. Thus, the mucous gland index was determined at two levels of the vestibular fold in each larynx, equivalent across the two groups.

RESULTS

The mucous gland indices calculated from the measurements are listed in the Table. The mean mucous gland index (± SD) for the 13 SIDS larynges was 19.52 ± 8.56. The average for the ten controls was 12.56 ± 6.25. The difference is significant statistically ($t = 3.00$; $P < .01$; two-tailed Student's t test), assuming both samples

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Fraction of Cross-sectional Area of Vestibular Fold Occupied by Mucous Glands in Sudden Infant Death Victims and in Infants Who Died of Other Causes

Sudden Infant Death Syndrome			Control			
Specimen No.	Mucous Index*	Sex/Age	Specimen No.	Mucous Index†	Cause of Death	Sex/Age
75	26.23 14.41	F/3 mo 17 days	76.51	7.28 7.75	Cystic fibrosis	F/3 mo 6 days
36	10.70 25.54	M/1 mo 6 days	75.11	17.99	Goldenhaar syndrome	M/2 mo 2 days
35	20.03 21.79	M/4 mo 2 days	65.14	5.86 5.97	Cystic fibrosis	M/13 days
22	16.32 10.98	M/3 mo 29 days	75.13	20.29 24.58	Periventricular leukomalacia	M/4 mo
34	17.95 18.61	F/3 mo 17 days	77.15	6.55 3.25	Congenital heart disease	M/1 day
31	16.17 31.99	M/2 mo 21 days	77.19	16.32 6.99	Biliary atresia	F/7 mo
646	6.47 10.48	M/1 mo 30 days	77.14	21.57 16.84	Congenital heart disease	F/4 mo 14 days
642	30.42 22.33	M/2 mo 22 days	77.47	17.63 12.73	Congenital heart disease	M/2 mo 22 days
643	31.11 38.85	F/4 mo 17 days	77.56	14.99 7.19	Cerebral hemorrhage	M/1 mo 11 days
644	2.73 18.63	M/3 mo 16 days	77.98	12.31 11.41	Fulminant meningitis	F/1 mo 3 days
654	19.75 19.70	M/2 mo 21 days				
661	19.53 26.67	M/1 mo 3 days				
672	23.0 7.0	M/1 mo 10 days				

*Mucous index is ratio of area of mucous glands to area of vestibular fold, ×100. Measurements were made at the top and bottom of the left vestibular fold of each larynx. For the 13 SIDS samples, mean ± SD was 19.52 ± 8.56 (t = 3.00, 21 df, $P < .01$ [two-tailed]).

†Mean ± SD was 12.56 ± 6.24 (n = 10).

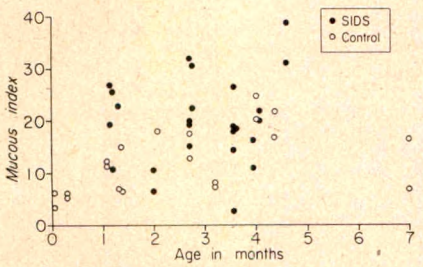

Fig 1.—Distribution of laryngeal mucous gland index in relation to age in victims of sudden infant death syndrome (SIDS) and in controls. Mucous gland index indicates the ratio of area of mucous glands to area of vestibular fold, times 100.

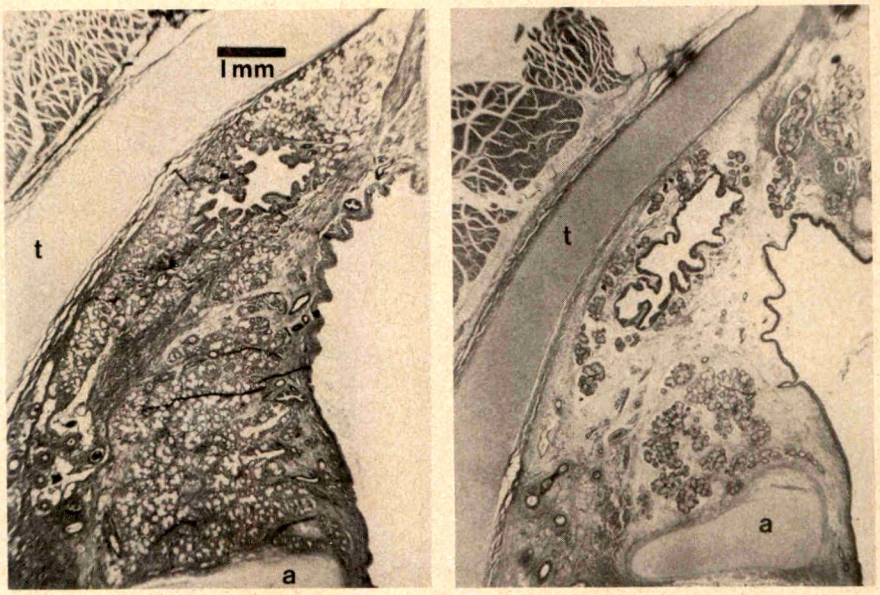

Fig 2.—Cross sections through the upper part of the left vestibular fold (hematoxylin-eosin, ×25); left, sudden infant death syndrome (SIDS); right, control. Point a indicates arytenoid cartilage; t, thyroid cartilage. Note apparent excess development of glandular acini in the SIDS specimen.

are drawn from normal distributions (Fig 1).

To test the significance of the data in the absence of an assumption concerning distribution, the nonparametric Mann-Whitney U test[8] was applied. On the H_1 hypothesis that the larynges from SIDS contained more mucous vestibular glands than the controls (two-tailed test), the calculated value of U was 147.5, the value of Z was −2.49, and the associated probability .0064. The H_1 hypothesis is therefore accepted.

Representative cross sections from a SIDS larynx (SIDS 643) and a control larynx (77.56) at the lower level of the vestibular fold are shown in Fig 2. The cells of the glandular acini were equally well defined in the two series. There was no suggestion of swelling or of inflammatory infiltration.

COMMENT

An exact inventory of the amount of mucous glandular tissue in the

larynx is not available. *Gray's Anatomy* states that mucous glands to the number of 60 or 70 open into the saccule.

The general topography of the mucous glands of the larynx was reviewed by Heiss.[9] He distinguished an anterior epiglottic, a middle or vestibular, and a posterior or interarytenoid group, and noted that the vestibular group is particularly well developed. Nassar and Bridger[10] suggested that, histologically, the glands are segregated into groups that are able to influence the spread of cancer, but these authors did not attempt to establish numerical measurements for the glandular densities. We found no information on this point, either in the adult or the infant, in the literature. In the present study, only the vestibular and epiglottic groups were counted, but corresponding regions of these groups were sampled in all specimens.

In our series, the SIDS victims ranged in age from 1 month and 3 days to 4 months and 17 days, and the controls from 1 day to 7 months. Great difficulty was experienced in obtaining permission for control specimens. The inclusion in the control group of specimens from two very young infants (1 day and 12 days, respectively) raises the possibility that immaturity was partly responsible for the low mean value of the controls. However, this seems unlikely, as the mucous gland index in the oldest control was about the same as in the youngest. The causes of death in the controls did not become available until after the measurements were complete. Two cases of congenital cystic fibrosis were included in the controls, but there is no indication that this biased the result of the assay. Three of the controls had undergone orotracheal intubation before death: one for a period of four days (76.51), one for two days (65.14), and one for a short period one week before death (77.56). Although mechanical irritation might have induced excessive mucus production, there was no indication that this occurred (Table).

The measurements indicate that the proportion of mucous glandular tissue or mucus in the vestibular folds of SIDS victims was half again as large as in the control group. An increase in the mucous content of acini may be present in Fig 2, left, and comparison suggests that the difference between the SIDS and the control specimens in general may reside in the burden of mucus borne by the glands rather than in the number of glands. The functional importance of the excess is not clear, but it seems reasonable to suppose that it may represent a correspondingly excessive secretion of mucus in the SIDS victims.

The possible bearing of such excess on previously suggested mechanisms of SIDS demands consideration. It is probably pertinent that many experienced anesthesiologists believe excess of mucus in the larynx predisposes to the development of laryngeal spasm if the subject is in a light plane of anesthesia.

One type of apnea, laryngeal spasm, has of course long been postulated as a contributing factor of SIDS,[11-13] and depression of the CNS in sleep with or without periodic apnea as described by Steinschneider[5] and by Guilleminault et al[6,14] might well predispose to a prolonged reflex laryngeal closure response similar to that encountered in the lightest plane of general anesthesia. Angell-James and Daly[15] described reflex apnea and bradycardia in anesthetized dogs secondary to stimulation of receptors in the nose and larynx. They considered this to be a potential mechanism in SIDS. The present results provide a further link in this speculative chain by providing a potential source of abnormal reflex stimulation, namely, excess mucus secreted by the glands of the larynx.

As is well known, there is reason to suspect that minor respiratory inflammatory events predispose the infant to SIDS[1] and such infections might well implicate the mucous glands and intensify their rate of secretions; gross signs of inflammation were not present in our specimens. Thus, the likelihood remains that SIDS may be the common outcome of several different mechanisms.[15,16]

Another factor predisposing to the syndrome may be the shape of the infant larynx. The hoodlike or semiconical shape of the infant epiglottis may be related to the relatively close proximity of the infant larynx to the hyoid bone. This shape occurs transiently in the adult during swallowing, and in the infant perhaps reflects a protective condition of partial closure adaptive to the high frequency of swallowing during sucking.[17] With maturation, the epiglottis gradually becomes straighter, the larynx descends, and the entrance opens more. This maturational aspect of laryngeal biomechanics may contribute to the characteristic age incidence of SIDS, which drops sharply by the sixth month.

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References

1. Beckwith JB: The sudden infant death syndrome. *Curr Probl Pediatr* June 1973, pp 1-36.

2. Naeye RL: Hypoxemia and the sudden infant death syndrome. *Science* 186:837-838, 1974.

3. Naeye RL: Pulmonary arterial abnormalities in the sudden-infant-death syndrome. *N Engl J Med* 289:1167-1170, 1973.

4. Kendeel SR, Ferris JAJ: Apparent hypoxic changes in pulmonary arterioles and small arteries in infancy. *J Clin Pathol* 30:481-485, 1977.

5. Steinschneider AL: Prolonged apnea and the sudden infant death syndrome: Clinical and laboratory observations. *Pediatrics* 50:646-654, 1972.

6. Guilleminault C, Peraita R, Souquet M, et al: Apnea during sleep in infants: Possible relationship with sudden infant death syndrome. *Science* 190:677-679, 1975.

7. Fink BR: Spring mechanisms in the human larynx. *Acta Otolaryngol* 77:295-304, 1974.

8. Siegl S: *Nonparametric Statistics*. New York, McGraw-Hill Book Co, 1956, p 116.

9. Heiss R: Der Kehlkopf, in von Mollendorff W (ed): *Handbuch der Mikroskopischen Anatomie des Menschen*. New York, Springer Verlag, 1966, vol 5, pp 728-742.

10. Nassar VH, Bridger GP: Topography of the laryngeal mucous glands. *Arch Otolaryngol* 94:490-498, 1971.

11. Handforth CP: Sudden unexpected death in infants. *Canad Med Assoc J* 80:872-873, 1959.

12. Shaw EG: Sudden unexpected death in infancy syndrome. *Am J Dis Child* 116:115-119, 1968.

13. Downing SE, Lee JC: Laryngeal chemosensitivity: A possible mechanism for sudden infant death. *Pediatrics* 55:640-649, 1975.

14. Guilleminault C, Araiagno R: Sudden infant death syndrome. *Bull Eur Physiopathol Respir* 13:591-597, 1977.

15. Angell-James JE, Daly MB: Some aspects of upper respiratory tract reflexes. *Acta Otolaryngol* 79:242-252, 1975.

16. Langston C: Sudden infant death syndrome. *Human Pathol* 7:492-494, 1976.

17. Fink BR, Martin RW: Biomechanics of the human epiglottis, abstracted. *Acta Otolaryngol* 87:554-559, 1979.

Breast-feeding and *Salmonella* Infection

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• **Various assays were used to examine chemotaxis, opsonization, phagocytosis, and killing of *Salmonella* organisms by colostral and breast-milk components. Vigorous responses of colostral and milk cells against this organism and nonspecific opsonizing capacity of the aqueous phase of colostrum and milk were demonstrated. An assay with acridine orange was used to directly visualize the phagocytic and killing processes; colostral and milk cells were demonstrated to be more active against *Salmonella* than blood neutrophils. In a restrospective survey, a diagnosis of *Salmonella* infection was confirmed in 253 infants less then 1 year of age. Only 12 infants had ever been breast-fed, and only one near the time he had the disease. During the same period of time, 27% of matched control infants were breast-fed.**

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There is increasing epidemiologic data supporting the contention that breast-feeding protects infants from gastrointestinal (GI) infection.[1-5] More recently, immunologic in vitro data have demonstrated various host defense mechanisms intrinsic to colostral or breast-milk components, and clinical correlates for these in vitro observations are apparent.[6-8] Human milk may therefore provide basic and often essential aspects of immunity for the neonate whose host defense mechanisms are deficient as determined by many measurements.[9]

The relationship of feeding methods to colonization with some specific GI pathogens has also been investigated. Recovery of attentuated polio viruses,[10] enteropathogenic *Escherichia coli*,[11-13] and *Shigella*[14] were all decreased in breast-fed as compared with bottle-fed infants. The clinical importance of the former two infectious agents has of course decreased notably during the past ten to 20 years. On the other hand, the reported incidence of *Salmonella* GI infection for infants in the United States has actually increased during the past decade.[15] No explanation for this increase is readily apparent. However, during the same period of time, a decline in the practice of breast-feeding has occurred.[3] To test the hypothesis that these developments are related, the present study was designed to examine feeding histories of young infants with *Salmonella* infection and to further evaluate immunologic mechanisms in host colostrum and milk specific for salmonellae.

MATERIALS AND METHODS

Population Studied

Isolations of salmonellae from infants less than 1 year of age in Arkansas during the two-year period from Jan 1, 1977 to Dec 31, 1978 were reviewed. Sources for cases included the epidemiology division of the Arkansas State Health Department, Little Rock, the microbiology laboratory of Arkansas Children's Hospital (ACH), Little Rock, and review of medical records from ACH and the University of Arkansas Hospital, Little Rock. These two hospitals represent the largest medical care facilities for children in the state of Arkansas. Mothers of infected infants were contacted by telephone to determine whether the infants had been breast-fed and, if so, for how long.

Data on general breast-feeding practices were obtained from two populations of mothers, subsequently referred to as clinic and private patients. The clinic group were delivered of their infants at the University of Arkansas Hospital and subsequently received routine care for their children at ACH; this is preponderantly a welfare population. Information regarding private patients was obtained from seven private practices in rural and urban areas throughout the state of Arkansas. In both clinic and private groups, medical charts were reviewed and mothers were questioned either during clinic visits or by telephone to ascertain the length of time they nursed their infants. Approximately 200 cases from the clinic and each private practice were evaluated in this manner.

Collection of Colostral and Milk Samples

Colostrum and milk were obtained from 60 healthy, lactating mothers sequentially at various postpartum periods. Samples were collected by manual expression or with a breast pump and were placed in sterile plastic containers. These were

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transported at room temperature and were examined in the assays described below within two hours.

Separation of Peripheral Blood Leukocytes

Heparinized peripheral blood was obtained from normal donors, and neutrophils were separated by 6% dextran sedimentation. Cells were washed twice, quantitated, and resuspended in appropriate medium. Essentially, assays with these peripheral blood neutrophils served as a basis of comparison for data from colostral and milk cells.

Preparation of *Salmonella* Suspension

Salmonella enteritidis, serotype *paratyphi* B originally isolated from a patient with gastroenteritis, was divided into equal portions in trypticase soy broth (TSB) and stored at −70 °C. These aliquots were quantitated by a standard colony count method so that when thawed, reconstituted with a fourfold volume of TSB, and grown at 37 °C for 18 hours, concentrations of bacteria were consistently 1 to 2×10^7 colony forming units per milliliter.

Quantitation of the Cellular Components in Colostrum and Breast Milk

After measuring volume, samples of colostrum and milk were centrifuged at 500 g for 20 minutes at 12 °C. During centrifugation, milk separates into three layers: a cell pellet, a middle layer, and an upper fat layer. The middle layer or aqueous phase was aspirated and stored for studies of opsonization, and the cell pellet was washed three times by centrifugation and was resuspended in Gey's solution. Total cells were quantitated in a hemocytometer. Differential counts were accomplished by preparing a monolayer stained with 0.14% acridine orange and by examining this preparation under fluorescence microscopy. In preliminary studies, differential counts of cytocentrifuged specimens stained with Wright-Giemsa, or nonspecific esterase stains, were more difficult to evaluate. Viability was determined using the trypan blue exclusion method.

Assays of Neutrophilic and Macrophagocytic Function

The following functional properties of colostral and milk neutrophils and macrophages were assayed: chemotaxis, reduction of nitro blue tetrazolium (NBT) dye, and phagocytosis and killing of *Salmonella* bacteria. Chemotaxis of neutrophils and macrophages was measured using the method of migration of cells under agarose gel.[16] In these assays, zymosan was used to activate chemotactic factors from complement. Spontaneous and endotoxin-stimulated NBT dye reduction was performed using the semiquantitative slide method.[17]

Phagocytosis and killing of *Salmonella* bacteria were first measured by the bactericidal method of Quie et al.[18] An assay using acridine orange as a vital stain for bacteria was then used to directly visualize phagocytic and killing processes and to differentiate the effects of neutrophils and macrophages. Live bacteria stain green with acridine orange; the color changes to bright red when the bacteria are killed by phagocytes.

Details of this assay were previously reported.[19] Briefly, monolayers were first prepared by placing five drops of colostrum, milk, or peripheral blood onto flat, glass coverslips and allowing attachment of these cells during an incubation of one hour at 37 °C in 5% CO_2. The supernatant fluid was then removed by gentle washing with normal saline solution, and two drops of *Salmonella* bacterial suspension containing approximately 1×10^8 of bacteria per milliliter in phenol-free Hanks' balanced salt solution with 10% fetal calf serum was placed on the cell monolayers. Coverslips were then incubated on a shaker at 37 °C for 90 minutes. After incubation, monolayers were washed twice with normal saline solution and stained for one minute with 0.14% acridine orange in Gey's solution. Coverslips were mounted face down and examined by fluorescence microscopy. Approximately 100 neutrophils and 100 macrophages were counted, and the total number of bacteria phagocytized was recorded as well as percent killed (red) and alive (green). A phagocytic index was calculated by dividing the total number of intracellular bacteria by the number of phagocytes counted.

Opsonization by Colostrum and Milk

The aqueous phase of colostrum and milk was examined for opsonizing capacity using peripheral blood neutrophils in two assay methods: the bactericidal method of Quie et al[18] and the chemiluminescence assay.[20]

Table 1.—Breast-feeding Practices and *Salmonella* Infection in Infants Less Than 1 Year Old

Population Surveyed	Total Births in Arkansas, Jan 1, 1977-Dec 31, 1978	% Breast-fed	Reported Incidence of *Salmonella* per 1,000 Infants		Significance
			Breast-fed	Bottle-fed	
University clinic	6,000	15	0.00	14.3	$P < .001$
Private	66,000	29	0.05	3.8	$P < .001$
Total	**72,000**	27	0.05	4.8	$P < .001$

RESULTS

Salmonella Infection in Infants

From Jan 1, 1977 to Dec 31, 1978 approximately 72,000 infants were born in the state of Arkansas. During this two-year period, 253 cases of *Salmonella* infection in infants less than 1 year of age were reported, 73 from the university clinic population and 180 from private practices (Table 1). Only one of these infants was being breast-fed at the time of clinical infection. Twelve infants were breast-fed sometime during the first year of life, but such feedings were discontinued an average of four months prior to documentation of *Salmonella* gastroenteritis or sepsis. The shortest interval was one week from discontinuation of breast-feeding to the onset of infection; this represents the single infant whom we considered being breast-fed at the time of infection. Table 1 therefore demonstrates that the incidence of *Salmonella* disease was significantly higher in bottle-fed than breast-fed infants. This difference was greater for clinic patients. The incidence in bottle-fed clinic patients was 14.3 cases per 1,000 infant population as compared with 3.8 per 1,000 in the private population.

Most cases of *Salmonella* infection occurred during the first few months of infancy; 75% of reported cases in this series were actually less than 6 months of age (Fig 1). These included three cases of *Salmonella* meningitis aged 5, 7, and 8 weeks. None of these three patients had sickle cell disease or other predisposing factors.

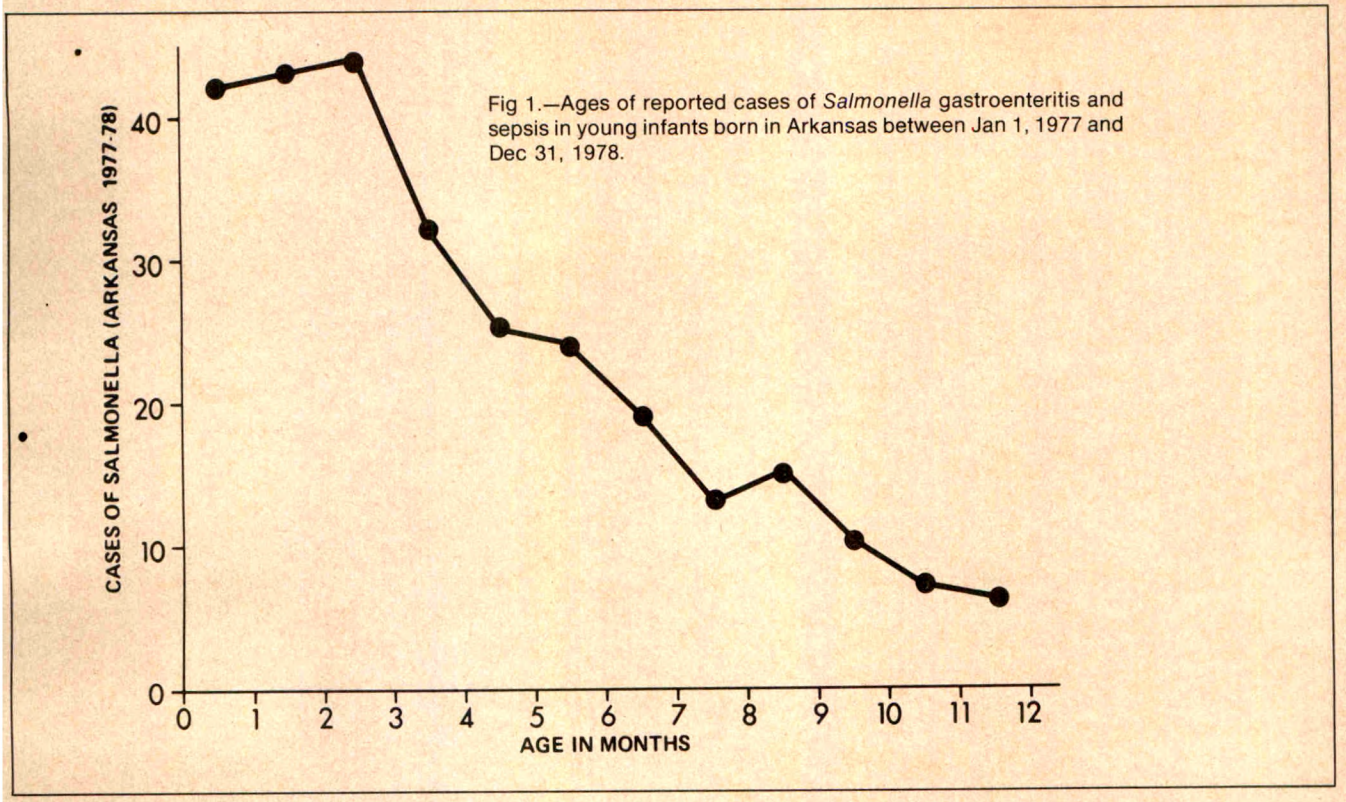

Fig 1.—Ages of reported cases of *Salmonella* gastroenteritis and sepsis in young infants born in Arkansas between Jan 1, 1977 and Dec 31, 1978.

Breast-feeding Practices

Fifteen percent of the clinic population breast-fed their infants as compared with 29% followed up in private practices. Both groups who breast-fed continued for an average duration of four months and this average varied little among seven private practices surveyed. Almost all mothers who elected to breast-feed their infants had discontinued the practice after six months. The percentage of infants breast-fed at various ages for our total population is summarized in Fig 2.

Immunologic Considerations

Total cell counts in colostrum and milk with absolute neutrophil, macrophage, and lymphocyte counts were determined sequentially for 60 healthy lactating women, and results are presented in Fig 3. Neutrophil and macrophage counts are greater than 1×10^7/mL in initial colostral samples, decreasing to 1×10^6/mL by the fourth postpartum day. Subsequently, cell counts remain less than 1×10^5/mL for the duration of lactation. Neutrophils are slightly more prevalent than macrophages until the fourth postpartum day, after which time macrophages constitute approximately 55% of the total cell content. Breast engorgement did not seem to influence total or neutrophil cell counts. Colostral and breast-milk samples from nonnursing mothers, one to four days postpartum, obtained during pumping for painful engorgement, showed counts similar to those from breast-feeding mothers.

Colostral and breast-milk cells did not respond to chemotactic factors generated from complement in fresh whole serum. Moreover, neither the aqueous phase of colostrum nor the aqueous phase of milk seem to contain enough complement or other chemotactic factors to influence the migration of peripheral blood neutrophils.

Resting metabolic activity in colostral neutrophils and macrophages was greater than for peripheral neutrophils as measured by the NBT Assay. An average of 24% (range, 11% to 34%) of colostral neutrophils and 19% (7% to 36%) of macrophages were NBT-positive as compared with 9% (2% to 17%) of blood neutrophils. Endotoxin increased the percent of NBT-positive colostral neutrophils to 56% (51% to 62%) but did not increase the percentage of NBT-positive macrophages; peripheral blood neutrophils in stimulated preparations average 72% (55% to 90%) positive cells.

Both bactericidal assays demonstrated vigorous phagocytic and killing capacity of colostral and milk cells against *Salmonella* organisms (Tables 2 and 3). Activity was comparable to peripheral neutrophils with the colony count method (Table 2), but the acridine orange assay, a bacteria-saturated system (Table 3), indicated that breast cells phagocytize more bacteria than peripheral neutrophils. Macrophages seem more active than breast neutrophils for both phagocytizing and killing of *Salmonella* organisms.

Opsonization of *Salmonella* bacteria by the aqueous phase of colostrum and milk as measured in the chemiluminescence assay appears in Fig 4. The initial rate of chemiluminescence is not as rapid as with whole fresh serum but is comparable to results with inactivated serum. Heating of colostrum or milk to 56 °C for 30 minutes does not alter this opsonizing capacity.

COMMENT

The present study was designed to comprehensively examine all aspects

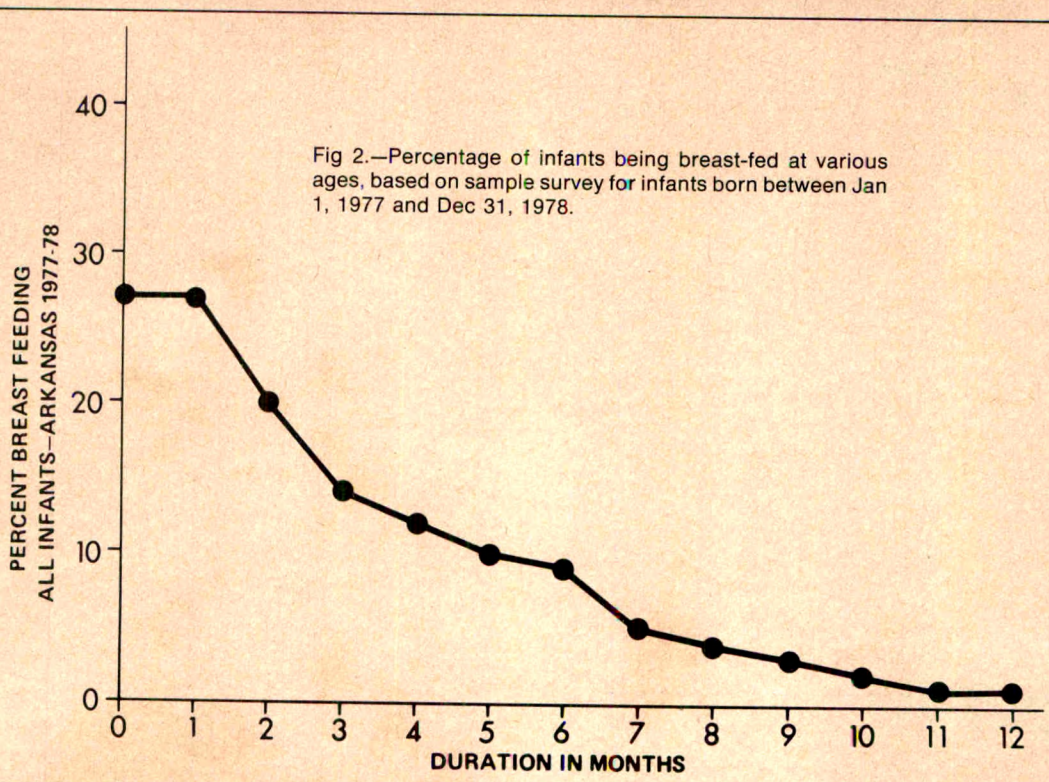

Fig 2.—Percentage of infants being breast-fed at various ages, based on sample survey for infants born between Jan 1, 1977 and Dec 31, 1978.

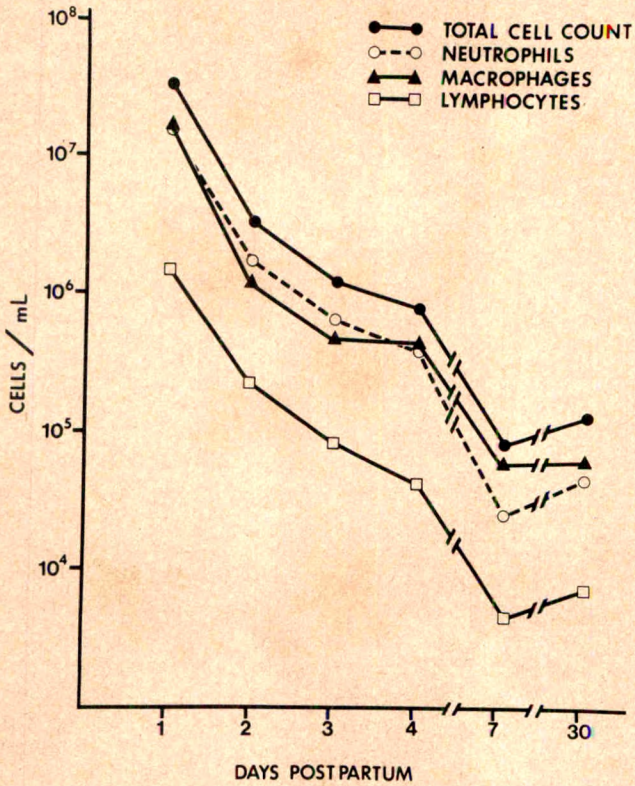

Fig 3.—Geometric mean concentration of total cells, neutrophils, macrophages, and lymphocytes in colostral and milk samples collected sequentially from 60 lactating donors.

of phagocytic function from their migration into colostrum and breast milk to final killing of a specific pathogen. By most in vitro variables evaluated, these phagocytic cells were active against *Salmonella* organisms and therefore seem to provide important mechanisms of host defense for the breast-fed infant. Such data was anticipated since *Salmonella*, an intracellular bacterium, is particularly susceptible to macrophagocytic killing processes.

Results determining the cellular content in colostrum and milk are similar to those reported previously[6,8,21] although some investigators have not observed high concentrations of neutrophils.[22,23] In the latter reports, either Wright-Giemsa or nonspecific esterase stains of cytocentrifuged specimens were examined. Often, these methods result in fragmenting of the neutrophils; moreover, differential counts based on cellular morphology are difficult with these stains. We found more consistent and more interpretable results using an acridine orange stain of living cells in a monolayer.

Unlike peripheral neutrophils and monocytes, colostral and breast-milk

Table 2.—Killing of *Salmonella* After Opsonization With Serum Using the Colony Count Method

Cell Source	% Killing (n = 9) Mean, %	SD, %
Peripheral blood	95.7	4.1
Colostrum	94.5	9.6
Milk	91.2	8.3

Table 3.—Phagocytosis and Killing of *Salmonella* by Colostral and Breast-Milk Cells*

Cell Type	Peripheral Blood Phagocytic Index†	Peripheral Blood % Killing	Colostrum Phagocytic Index	Colostrum % Killing	Milk Phagocytic Index	Milk % Killing
Neutrophils	1.9	87	3.5	73	2.5	55
Macrophages	. . .	. . .	4.7	99	3.2	84

*Using the acridine orange staining method.
†Total number of intracellular bacteria divided by number of cells counted.

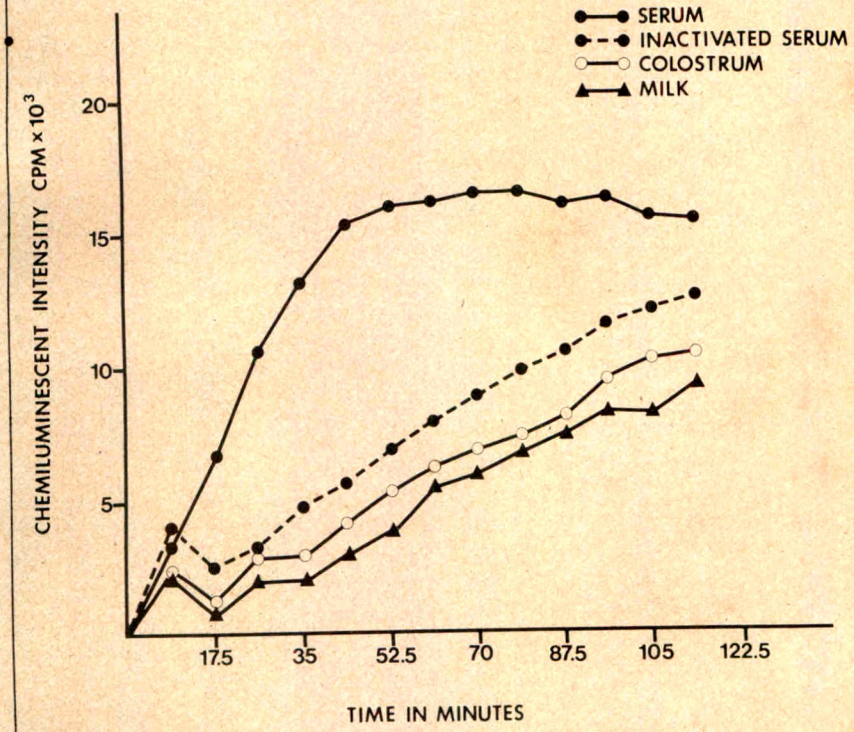

Fig 4.—Temporal traces of chemiluminescence from 5 × 10^6 polymorphonuclear leukocytes after the addition of *Salmonella enteritidis*, serotype *paratyphi* B, which was first opsonized with various fluids. Bacteria added to buffer alone and then combined with leukocytes yielded no chemiluminescent response at any time interval studied. CPM indicates counts per minute of photoemission.

cells do not respond to chemotactic factors in vitro. Breast milk itself contains only low concentrations of complement components such as C3 and C4,[13] probably too low to generate adequate chemotactic factors in vivo to influence migration of neutrophils or macrophages. If the complement was present in substantial quantities, its heat and acid liabilities would render it nonfunctional once reaching the infant's GI tract. Components other than complement in breast milk, which might provide chemotactic activity, have not been described.

The elevated resting values for the NBT dye reduction assay indicate that phagocytes in colostrum and breast milk are more metabolically active than those in peripheral blood. This may be the result of the active phagocytosis of fat particles by breast-milk cells. Also, essentially all colostral and milk samples are colonized by bacteria regardless of the care in collection, and such contamination may elevate phagocytic and thus metabolic activity.

Neither aqueous phase colostrum nor milk opsonize *Salmonella* for phagocytosis by peripheral neutrophils using the standard colony count assay. However, opsonization was appreciated in the chemiluminescence assay. Methodology alone may account for the discrepant results. In the colony count assay, a bacteria-to-cell ratio of 1:1 is used whereas in the chemiluminescence assay, the preparation is saturated with bacteria, yielding a ratio of approximately 100 bacteria per phagocyte. The latter assay allows optimal contact for phagocytes and bacteria. Modifications of the colony count assay have been used with other bacteria, and opsonization by aqueous phase milk or colostrum has been demonstrated.[7] Other studies using this assay have demonstrated that colostrum and milk actually protect bacteria from the effects of phagocytic cells.[6]

The clinical data in this study also strongly support a major role for breast-feeding in protection against *Salmonella*. Breast-fed infants have a significantly ($P < .001$) lower incidence of infection. The only alternative possibility is that other aspects of care for breast-fed infants are in some way different so that contact with *Salmonella* bacteria is decreased. To examine this hypothesis, the source of *Salmonella* exposure in infants must be determined. Unfortunately, this information is not generally reported to the Center for Disease Control, Atlanta, or other surveillance programs. The common modes of transmission including contaminated food, water, household pets, and person-to-person contact have rarely caused recognized outbreaks in infants. Environmental cultures were obtained in many of the present cases. Samples of

the water supply were all negative, and only occasionally was *Salmonella* cultured from the mother or other family members. Certainly, a prospective study designed to examine various aspects of infant feeding and care might delineate a source of infection, and such a study is currently in progress at our institution.

The highest incidence of *Salmonella* infection occurred during the first few months of life (Fig 1). This is an important observation since most mothers prefer to nurse their infants for just a few months (Fig 2). Therefore, considering the present protection data, recommendations need not emphasize breast-feeding for long periods of time. Furthermore, because the feedings of many breast-fed infants in the present study were supplemented with bottle feedings, the resulting partial breast-feeding seems to offer equally effective protection from *Salmonella* infection. On the other hand, such protection from *Salmonella* lasts only while breast-feeding is continued; 12 infants who were nursed for some period of time subsequently became infected after breast-feeding was discontinued.

Breast-feeding is not the only factor influencing propensity to *Salmonella* infection. If it were, a higher incidence would be expected after women cease nursing their infants. Since this was not noted, other factors must play a role. Such factors would include increased susceptibility of the extremely young infant secondary to either inadequate host responses or to increased exposure from an environmental source.

Previous studies have demonstrated that the protective properties of breast milk are more evident among the lower socioeconomic segment of the population. Similarly, our data show greater protection of breast-feeding for a defined welfare population as compared with a preponderantly middle class group. Some differences in our incidence of *Salmonella* for clinic vs private patients must be attributed to methods of reporting. This study was primarily conducted by investigators serving the university clinic population, and it is expected that reporting and follow-up of these patients was better. It is doubtful, however, that the almost fourfold greater incidence in the university clinic population could be accounted for by reporting practices alone. We therefore conclude that breast-feeding should be encouraged particularly for the lower socioeconomic segment of our population. Unfortunately, the trend has been just the reverse. Actually, fewer mothers in this socioeconomic group breast-feed as demonstrated in the present study (Table 1).

Three cases of *Salmonella* meningitis were recognized during the study period, and all cases were in infants less than 3 months of age. Thus, one out of every 40 cases of *Salmonella* infection in the 0- to 3-month age group resulted in systemic dissemination. Aggressive treatment and follow-up of the extremely young infant with *Salmonella* infection is certainly warranted.

A decline in the practice of breast-feeding during the previous two decades may have contributed to an increased incidence of *Salmonella* infection in infants. This association may also apply to other GI and respiratory pathogens. Pediatricians should therefore strongly consider host resistance factors provided by breast milk in formulating their approach to antepartum counseling. There is additional reason to particularly encourage routine breast-feeding for the lower socioeconomic populations in this country.

This project was started by the Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, to acknowledge active participation in the International Year of the Child, 1979. Janet Schneider provided editorial assistance. Paul C. White, Jr, MD, epidemiologist and Director of Communicable Disease Control for the state of Arkansas, provided *Salmonella* epidemiologic data.

References

1. Larsen SA Jr, Homer DR: Relation of breast versus bottle feeding to hospitalization for gastroenteritis in a middle-class US population. *J Pediatr* 92:417-418, 1978.

2. Cunningham AS: Morbidity in breast-fed and artifically fed infants. *J Pediatr* 90:726-729, 1977.

3. Barness LA, Mauer AM, Anderson AS, et al: Breast-feeding: A commentary in celebration of the international year of the child, 1979. *Pediatrics* 62:591-601, 1978.

4. Hanson LA, Winberg J: Breast milk and defense against infection in the newborn. *Arch Dis Child* 47:845-847, 1972.

5. Mata LH, Urrutia JJ, Gordon JE: Diarrheal disease in a cohort of Guatemalan village children observed from birth to age 2 years. *Trop Geogr Med* 19:247-251, 1967.

6. Ho PC, Lawton JWM: Human colostral cells: Phagocytosis and killing of *E coli* and *C albicans*. *J Pediatr* 93:910-915, 1978.

7. Robinson JE, Harvey BAM, Soothill JF: Phagocytosis and killing of bacteria and yeast by human milk cells after opsonization in aqueous phase of milk. *Br Med J* 1:1443-1445, 1978.

8. Ogra SS, Ogra PL: Immunologic aspects of human colostrum and milk. *J Pediatr* 92:550-555, 1978.

9. Miller ME: Host defenses in the human neonate. *Pediatr Clin North Am* 24:413-423, 1977.

10. Lepow ML, Warren RJ, Guay N, et al: Effect of Sabin type 1 poliomyelitis vaccine administered by mouth to newborn infants. *N Engl J Med* 264:1071-1075, 1961.

11. Hodes H: The etiology of infantile diarrhea. *Adv Pediatr* 8:13-19, 1956.

12. Neter E: Enteritis due to enteropathogenic *Escherichia coli*. *J Pediatr* 55:223-229, 1959.

13. Goldman AS, Smith CW: Host resistance factors in human milk. *J Pediatr* 82:1082-1090, 1973.

14. Mata LJ, Urrutia JJ, Garcia B, et al: *Shigella* infection in breast-fed Guatemalan Indian neonates. *Am J Dis Child* 117:142-146, 1969.

15. Fox MD, Loewenstein MS, Martin SM: *Salmonella* surveillance: 1970. *J Infect Dis* 125:196-198, 1972.

16. Nelson RD, Quie PG, Simmons RL: Chemotaxis under agarose: A new and simple method for measuring chemotaxis and spontaneous migration of human polymorphonuclear leukocytes and monocytes. *J Immunol* 115:1650-1654, 1975.

17. Feigin RD, Shackelford PG, Choi SC, et al: Nitroblue tetrazolium dye test as an aid in the differential diagnosis of febrile disorders. *J Pediatr* 78:230-237, 1971.

18. Quie PG, White JG, Holmes B, et al: In vitro bactericidal capacity of human polymorphonuclear leukocytes: Diminished activity in chronic granulomatous disease of childhood. *J Clin Invest* 16:668-674, 1967.

19. Smith DL, Rommel F: A rapid micro method for the simultaneous determination of phagocytic-microbicidal activity of human peripheral blood leukocytes in vitro. *J Immunol Methods* 17:241-249, 1977.

20. Allen RC: Evaluation of serum opsonic capacity by quantitating the initial chemiluminescent response from phagocytizing polymorphonuclear leukocytes. *Infect Immunol* 15:828-833, 1977.

21. Pittard WB III: Breast milk immunology: A frontier in infant nutrition. *Am J Dis Child* 133:83-87, 1979.

22. Smith CW, Goldman AS: The cells of human colostrum: I. In vitro studies of morphology and function. *Pediatr Res* 2:103-109, 1968.

23. Lascelles AK, Gurner BW, Coombs RRA: Some properties of human colostral cells. *Aust J Exp Biol Med Sci* 47:349-352, 1969.

Fibromuscular Hamartoma of the Esophagus in an Infant

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An 11-month-old infant had a history of dysphagia and continuous drooling without evidence for airway obstruction. A biopsy specimen of a neck mass on the left side adherent to the larynx and esophagus demonstrated pathologic features characteristic of a fibromuscular hamartoma. Upper airway obstruction subsequently ensued and the patient was managed for 16 months with a tracheostomy and feeding gastrostomy. Although posing an extremely difficult management problem, this benign tumor was surgically removed without damage to the larynx when the patient was 28 months old. The differential diagnosis of this unusual lesion must consider congenital fibromatosis and fetal rhabdomyoma.

(*Am J Dis Child* 134:153-155, 1980)

A hamartoma may be defined as an excessive focal growth of mature normal cells and tissues in an organ or tissue composed of identical cellular elements.[1] This type of benign developmental tumor rarely has been observed in infancy and childhood and in only four instances have such tumors been reported in the region of the trachea and esophagus in any age group.[2-5] We have recently diagnosed and surgically treated a fibromuscular hamartoma that compressed and obstructed both the cervical trachea and esophagus in an infant whose major initial symptom was dysphagia. This histologically benign tumor presented an extremely difficult management problem because of its location.

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REPORT OF A CASE

This 2-year-old boy was first hospitalized at 11 months of age because of failure to gain weight since 6 months of age. He was the product of a full-term uncomplicated pregnancy and was born weighing 3.2 kg after a normal labor and vaginal delivery. The neonatal course was unremarkable. He was breast fed and had no reported feeding difficulties during the first several months of life. He tolerated strained baby foods, but when "table foods" were added at two months of age he began to spit out most of what was fed to him. He continued to gain weight until approximately 6 months of age but then lost about a kilogram during the next five months. There was no history of excessive emesis or diarrhea. All solid foods were either refused or caused gagging. Drooling was incessant. He had two episodes of bronchitis during this first year of life. There was no history of stridor, pneumonia, or cyanosis with feeding. Physical examination showed a thin child whose weight was 6.38 kg (third percentile for age); height, 71 cm (tenth percentile for age); and head circumference, 44.5 cm (tenth percentile for age). The child constantly drooled copious amounts of saliva. There was a generalized decrease in subcutaneous fatty tissue. The auricular and oral cavities were unremarkable. There were shotty but firm posterior cervical and inguinal lymph nodes. The trachea was deviated to the right by a soft-tissue mass situated at the junction of the cricoid cartilage and trachea on the left side of the neck. The cry was qualitatively normal, but mild inspiratory stridor was heard over the trachea. Results of cardiopulmonary and abdominal examinations were normal. There were no neuromuscular deficits. Laboratory evaluation showed the following values: WBCs, 15,000/cu mm; hemoglobin, 12.4 g/dL; hematocrit, 37%; total serum proteins, 7.6 g/dL; albumin, 4.4 g/dL; BUN, 7 mg/dL; serum creatinine, 0.5 mg/dL; and glucose, 85 mg/dL. The chest roentgenogram (Fig 1) showed noticeable deviation of the trachea to the right at the level of C3-4. A cine-esophagogram showed pharyngeal incoordination with reflux of barium into the nasopharynx and a large posterior indentation of the esophagus at the region of the cricopharyngeus muscle (C3-4). A xeroradiograph of the neck showed deviation of the trachea anteriorly and to the right by a mass at the level of C3-4 (Fig 2). Bronchoesophagoscopy showed that the trachea was partially compressed and the esophagus was almost completely obstructed by the mass lesion.

The neck was explored via a collar-type incision and a firm mass was visualized at the junction of the trachea and larynx that displaced the trachea to the right and encompassed the esophagus posteriorly. Biopsy of the mass yielded fragments of whitish-tan hemorrhagic tissue. The pathologic report raised some questions as to whether the mass had actually undergone a biopsy. Therefore, a few days after the initial biopsy, the neck incision was reopened and another biopsy specimen obtained from deeper within the mass lesion.

Because of progressive airway obstruction after the biopsy, a tracheostomy and feeding gastrostomy were performed. The clinical course over the next 16 months was complicated by recurrent aspiration pneumonia that resulted in mild chronic interstitial lung disease. The tumor was completely resected when the patient was 28 months of age. Postoperative convalescence was unremarkable. The patient was discharged from the hospital and followed up closely for tracheostomy and gastrostomy care. Within four weeks of removal of the tumor, his swallowing function had improved dramatically and he was able to swallow liquids and foods; his gastrostomy tube was then removed. His tracheostomy tube has not yet been successfully removed because of a mucosal flap causing obstruction proximal to the tracheostomy stoma. However, placement of a small tracheostomy tube has allowed him to develop normal speech for his age.

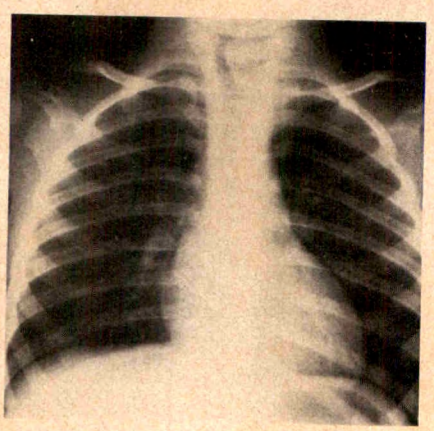

Fig 1.—Posteroanterior chest roentgenogram. Trachea is noticeably deviated to right at level of C3-4. Lung fields are clear.

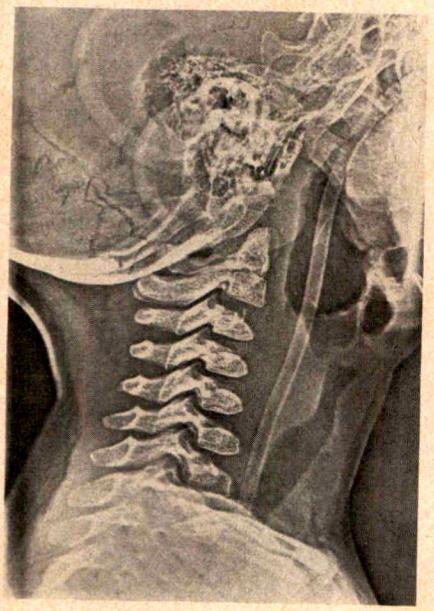

Fig 2.—Xeroradiographic examination demonstrates anterior bowing of tracheal air column at level of C3-5.

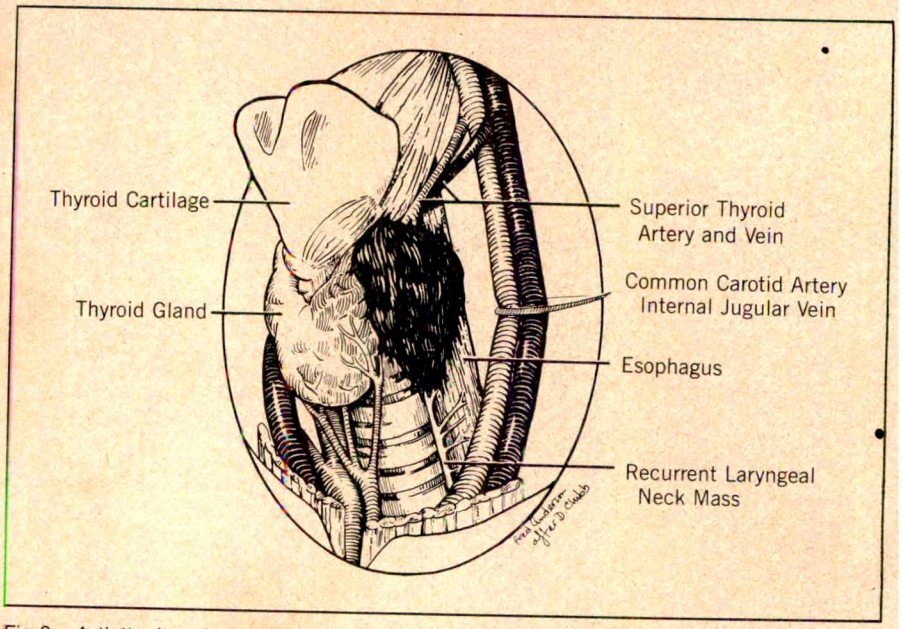

Fig 3.—Artist's description of tumor mass with respect to surrounding structures. Drawn from photographs obtained at surgery when mass was removed.

SURGICAL APPROACH

So as to minimize morbidity, an attempt at definitive extirpation of this tumor was delayed until the infant had grown more. The apparent attachment of the tumor mass to both the trachea and esophagus in the tracheoesophageal groove suggested that part or all of the larynx may have to be removed with the mass. At 28 months of age, after the child had grown, it was decided to remove the mass because of the recurrent pneumonias and persistent tracheoesophageal obstruction.

The tumor was again approached through an incision in the left side of the neck (Fig 3). The carotid sheath was retracted laterally, and the thyroid gland and the tumor attachments to the trachea and esophagus were identified. The tumor mass was gently delineated and dissected free from the larynx and trachea, leaving these structures intact. The major mass of tumor seemed to originate from the left lateral wall of the cervical esophagus. A portion of the esophagus and the superior lobe of the left thyroid were removed with the mass. The defect in the esophagus was closed. Examination of the remaining esophagus showed no evidence of residual tumor.

PATHOLOGIC FINDINGS

The initial biopsy specimen of the mass showed, on frozen and permanent sections, striated skeletal muscle with atrophic changes. The atrophic muscle bundles were surrounded by small oval to spindle-shaped mesenchymal cells resembling fibrous connective tissue of varying degrees of differentiation. The second biopsy specimen consisted of three small segments of whitish tan tissue with focal areas of hemorrhage. Histologically, the tissue had three mesenchymal elements: skeletal muscle fibers, fibrous connective tissue, and hyaline cartilage (Fig 4). The skeletal muscle consisted of mature muscle fibers arranged in a fascicular growth pattern. The fibrous connective tissue exhibited various degrees of maturity, and the hyaline cartilage and perichondrium were fairly immature in growth pattern. These findings presented the following two distinct diagnostic possibilities: either an exuberant young fibromatosis or a hamartomatous malformation. There was no evidence of malignant transformation in multiple sections.

The entire tumor mass was removed in two pieces of firm whitish yellow tissue, the largest measuring 2.5 × 1.5 × 1.5 cm. Multiple sections of this mass showed striated muscle fibers with varying degrees of differentiation. Cross striations were evident. The muscle fibers retained their fascicular pattern with interlacing of fibrous connective tissue. A segment of thyroid tissue adjacent to the muscle mass showed the main mass to be compressing it, with atrophy of adjacent follicles. There were several focal areas of muscle and connective tissue projections into the thyroid stroma. Cartilage was also observed and the surrounding tissue showed chronic inflammation and focal hemorrhage. A section through the esophageal mucosa and submucosal area showed

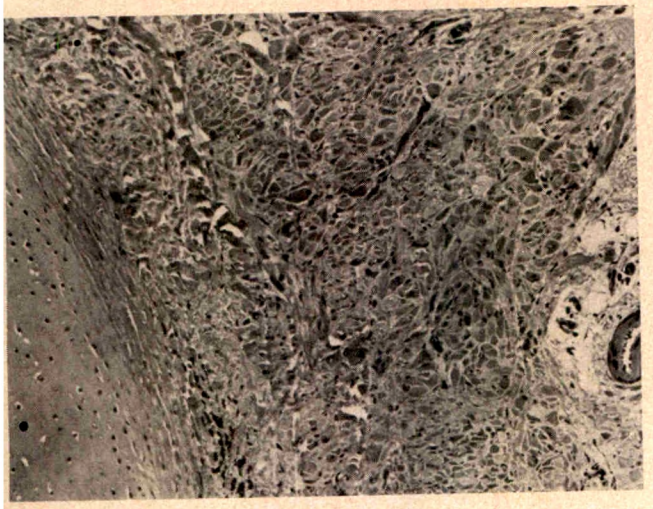

Fig 4.—Intermixture of skeletal muscle, fibrous connective tissue, and hyaline cartilage (hematoxylin-eosin, ×63).

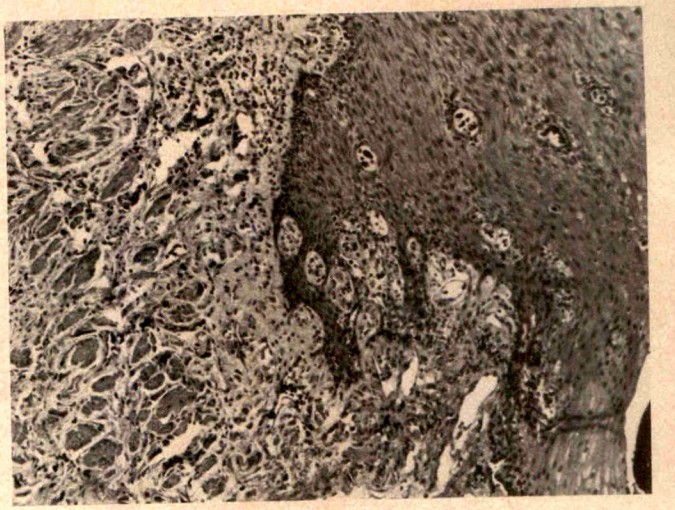

Fig 5.—Esophageal mucosa with fibromuscular tissue directly beneath (hematoxylin-eosin, ×63).

the tumor mass to lie directly beneath the mucosa (Fig 5).

COMMENT

Based on the presence of skeletal muscle, cartilage, and the peculiar and unexplained perineural-muscle changes, the lesion was classified as a hamartoma. Because of the infiltrative pattern noted, a form of congenital fibromatosis was also considered. However, the maturity of the muscle, the presence of the connective tissue in the periphery of the mass, and the presence of the cartilage were more suggestive of a hamartomatous lesion than a fibromatous malformation. A fetal rhabdomyoma was also considered, but because of the highly organized configuration of the skeletal muscle, this diagnosis was excluded. The pathologic slides were reviewed by the Armed Forces Institute of Pathology, Washington, DC, which concurred with the diagnosis of hamartoma by Franz M. Enzinger, MD (written communication, June 1978).

Hamartomas are uncommon benign developmental tumors that may occur in all organs of the body. Similar types of tissue normally exist in the region in which the hamartoma is found, but the tumor tissue has escaped organization and may be poorly differentiated and found in excess of what is to be expected. In hamartomas, the cellular components are usually mature showing no anaplasia but occasionally evidence of structural disorganization. It is for this reason that they are classified as congenital malformations. Many hamartomas do not have the ability for continuous growth and, therefore, can only be considered to be tumor-like malformations. There are others that do show progressive proliferation, a basic characteristic of a true tumor.

A review of the literature[2-5] shows scant information concerning congenital hamartomas in the cervical region. Stout and Lattes[5] discussed benign mesenchymomas, using hamartoma as one of the synonyms. They listed a number of lesions as mesenchymomas, including mixed mesenchymal tumors, angiomyolipomas lipomyomas, angiolipomas, and mesenchymal hamartomas.

Benign developmental tumors accounted for 71% (190/267) of a large series[6] of neck masses in infants and children and, thus, such tumors are relatively common. That study, however, did not report the occurrence of a single hamartoma. To our knowledge, hamartomas involving the cervical structures have only been reported previously in four patients, two of whom were children.[2-5] Three of the cases reported were polypoid intraluminal esophageal hamartomas, histologically composed of either gastric mucosa[2] and cartilage[2,3] or respiratory epithelium and fibrotic connective tissue.[4] The fourth case, a 3-month-old infant, had a tumor that histologically showed an admixture of myxoidchondromatous, lipomatous, and vascular components but no specific skeletal muscle tissue. Our patient's hamartoma, however, was composed of poorly differentiated striated muscle cells, cartilage, and fibrous tissue and appeared to originate from the external esophageal wall. It is interesting to note that after incomplete excision, recurrent tumors may consist of only one of the elements of the original tumor.

Hamartomas need to be considered in the differential diagnosis of neck masses in children. They may pose difficult management problems that often require emergency care. However, these tumors can be successfully removed without damage to the larynx.

Adele Goodberry provided secretarial assistance.

References

1. Robbins SL: *Pathologic Basis of Disease.* Philadelphia, WB Saunders Co, 1974, pp 128, 567.

2. Dieter RA, Riker WL, Holinger P: Pedunculated esophageal hamartoma in a child. *J Thorac Cardiovasc Surg* 59:851-854, 1970.

3. Shah B, Unger L, Heimlich HJ: Hamartomatous polyp of the esophagus. *Arch Surg* 110:326-328, 1975.

4. Fuller AP: Pedunculated hamartoma of the esophagus. *J Laryngol Otol* 77:706-713, 1963.

5. Stout AP, Lattes R: *Tumors of the Soft Tissues.* Atlas of Tumor Pathology, 2nd series, Washington, DC, Armed Forces Institute of Pathology, 1967, series 2, p 88.

6. Moussatos GH, Baffes TG: Cervical masses in infants and children. *Pediatrics* 32:251-256, 1963.

Naloxone

Underdosage After Narcotic Poisoning

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• A case of propoxyphene hydrochloride (Darvon) poisoning was unresponsive to therapeutic doses of naloxone hydrochloride in a 2½-year-old girl. Following prolonged coma and artificial ventilation for three hours, the patient responded immediately to the intravenous administration of 2 mg of naloxone hydrochloride, which is 20 times the manufacturer's recommended dosage. Naloxone is the agent of choice in reversing the effects of narcotics and synthetic opiate derivatives, such as propoxyphene and pentazocine. The manufacturer's present recommended dosage may not be sufficient to reverse the effects of large narcotic ingestions. We therefore recommend that if there is no response within two minutes of the initial 0.01 mg/kg dosage of naloxone hydrochloride, a second dose 0.1 mg/kg (ten times the manufacturer's suggested dose) be given.

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Naloxone hydrochloride is recommended for the reversal of narcotic-induced symptoms.[1] Numerous reports document naloxone's effectiveness in antagonizing the actions of a variety of narcotic drugs, including diphenoxylate hydrochloride,[2,3] propoxyphene hydrochloride,[4,5] pentazocine,[6] morphine,[7,8] and dextromethorphan.[9] Unlike levallorphan tartrate and nalorphine hydrochloride, which can produce severe agitation[8] as well as respiratory depression with reduced tidal volume and rate,[10] the only side effect associated with high-dose naloxone therapy in normal subjects has been a mild feeling of sleepiness.[11,12]

Since 31% of children in comas due to barbiturate ingestion are seen initially with miosis (88% in narcotic ingestion),[13] the advantage of using naloxone as opposed to other narcotic antagonists in a therapeutic trial is clear. No further respiratory compromise will be induced in patients with nonnarcotic poisonings. At present the manufacturer's recommended dose in children with suspected narcotic toxicity is 0.01 mg/kg of naloxone hydrochloride given intravenously (IV), intramuscularly, or subcutaneously[14] and repeated every two minutes as needed to a maximum of three dosages. As the following case history illustrates, a larger initial dose may be necessary.

REPORT OF A CASE

A 2½-year-old girl was in good health until noon on the day of admission, when she had a tonic-clonic seizure. During transport to Denver General Hospital, the child had two additional seizures and due to increasing respiratory distress, she was immediately intubated on arrival. An arterial blood sample revealed a pH of 7.21, a PO_2 110 mm Hg, and a PCO_2 of 42 mm Hg. A fourth seizure was controlled with 2 mg diazepam IV, and 10 g of glucose was given IV without clinical effects. Physical examination revealed a comatose child with miotic pupils; pulse rate was 110 beats per minute, respirations were 24/min, temperature was 37.2 °C, and blood pressure was 80/P. Although the mother strongly denied the possibility of drug ingestion, 0.1 mg of naloxone hydrochloride (0.01 mg/kg) was given IV without clinical response. Due to persistent ventricular tachyarrhythmias, the child then received 10 mg of lidocaine hydrochloride IV, with improvement of the arrhythmia. One and one-half hours after arrival in the emergency room, the child was transferred to pediatric intensive care where her stomach was lavaged with 2 L of normal saline followed by instillation of 15 g of activated charcoal and 2.5 g of magnesium sulfate.

Initial laboratory studies yielded a hematocrit value of 33% and a WBC count

of 20,000/cu mm, with 36% polymorphonuclear leukocytes, 1% basophils, and 55% lymphocytes. Results of automated chemical analysis with six- and 12-channel systems were within normal limits, except for a SGOT value of 65 units, a lactic dehydrogenase value of 280 units, and a serum alkaline phosphatase level of 265 units. The CSF was normal, and arterial blood gases were stable. The Rocky Mountain Poison Center suggested that 2 mg (20 times the recommended dose) of naloxone hydrochloride be administered IV. Clinical improvement was seen within seconds, and the child was active and alert within two minutes. She was extubated 30 minutes later and her condition remained stable throughout the night; she required only one further dose of 1 mg of naloxone hydrochloride.

That evening the toxicology laboratory reported that the gastric aspirate was strongly positive for propoxyphene and that the serum level was 0.45 mg/dL. Therapeutic levels of propoxyphene are less than 0.2 mg/dL and toxic symptoms occur at higher levels. The mother also reported that she found an open bottle of 65-mg tablets of propoxyphene hydrochloride (Darvon) under her dresser at home.

COMMENT

A comatose child brought to a busy emergency room can present a very perplexing problem. The history is frequently unreliable or misleading. The presence of constricted pupils should immediately alert the physician to the possibility of narcotic ingestion, but other drugs including phenothiazines, ethanol, and barbiturates as well as CNS injuries and infections can cause pupillary constriction.[13] The patient in our report did receive a single therapeutic trial of naloxone at the manufacturer's recommended dose. Owing to lack of clinical response, the physician decided to look elsewhere for an etiology of the child's seizures and coma. Had a larger initial dose of naloxone been given, the child may not have had to suffer three additional hours of coma and artificial ventilation.

The site of narcotic agonist and antagonist action is specific opiate receptors on the synaptic membranes of the amygdala, hypothalamus, and thalamus.[15,16] By combining with these receptors, the narcotic blocks the motivational-affective components of pain without affecting the sensory conponent. Naloxone and other narcotic antagonists are believed to act by competing for these receptor sites.[11,17,18] Therefore, the greater the amount of narcotic ingested the larger the amount of antagonist needed to competitively inhibit its effect. Antagonists have been found to reverse ten to 100 times the dose of narcotic. This is primarily due to enhancement of antagonist binding in the presence of sodium.[15,19] Since the receptors lie in the sodium-rich interstitial fluid, there is increased affinity for the antagonists compared with the agonists. In spite of this increased affinity, the point remains that the more narcotic taken the larger the amount of antagonist needed to reverse its effect.

High doses of naloxone in the normal subject produce only mild subjective side effects.[11,12] Nausea and vomiting frequently occur after an injection of naloxone in patients who have been under anesthesia[7] and occasionally with narcotic overdoses, but this response is not dose related. There have been recent reports of ventricular irritability[20] and hypertension[21] after the use of naloxone in patients who have undergone cardiac surgery, but again this is not considered to be dose related and a definite cause-effect relationship has not been established. Early studies of naloxone in man used as much as 20 mg IV[22] and 75 mg subcutaneously[23] as single doses without any adverse reactions. Rumack and Temple[2] reported the case of a 2½-year-old child who had ingested a mixture containing diphenoxylate hydrochloride (Lomotil) and inadvertently received 20 mg of naloxone hydrochloride IV (approximately 2 mg/kg or 200 times the recommended dose); the child's clinical response was good and no adverse effects occurred. Administration of doses up to 5.6 mg/kg in dogs has not resulted in adverse effects on the cardiovascular system.[24] The question remains why suggested initial recommended doses of naloxone are so small while the need for larger doses to obtain adequate clinical response has been previously recognized.[18] We suggest that the manufacturers revise their recommendations to indicate the administration of larger doses to patients who are unresponsive.

Our recommendation for the initial management of a comatose child with possible narcotic intoxication is to give an immediate trial dose of 0.01 mg/kg of naloxone hydrochloride (the manufacturer's recommended dose) followed in two minutes by 0.1 mg/kg of naloxone hydrochloride (ten times the manufacturer's recommended dose) if no clinical improvement is seen. Due to the lack of toxicity of naloxone, the dose should not be smaller than 0.1 mg/kg. In our experience, this dosage protocol has proven safe and effective in over 1,800 cases of narcotic ingestion in children since 1972, with no adverse sequelae. Therefore, all children who receive the initial 0.01 mg/kg dose and show no response must receive the second larger dose or the therapeutic trial is incomplete. If the child is convulsing, anticonvulsants should be withheld until this trial is completed, since further depression in respiratory status and state of consciousness may be produced by the anticonvulsant. Also, naloxone has been suggested as being therapeutic in the control of certain narcotic-induced seizures.[4] Since the half-life of naloxone is short[25] in comparison with the half-lives of most narcotics, the child needs to be observed closely for return of narcotic symptoms. Repeated doses of naloxone may be necessary until the narcotic is metabolized and excreted. If required, repeated doses of naloxone should be given in the same dose that produced initial reversal of symptoms.

The use of naloxone in older children or young adults with a history of narcotic use or evidence of addiction is a concern of most emergency room physicians. However, in our experience, the use of naloxone in addicts has resulted in a brief withdrawal syndrome without detrimental effects. The use of naloxone should not be withheld in situations where the patient is suspected of being an addict.

Emesis or lavage should always be performed since delayed gastric emptying is common following narcotic ingestions.[2] Emesis can be

induced in the alert patient, but if seizures or coma exist, tracheal intubation and gastric lavage with a large bore (28-French or larger) Ewald tube should be carried out. Activated charcoal, five to ten times the estimated weight of ingested drug (minimum of 10 g), as well as a nonabsorbable saline cathartic (sodium sulfate or magnesium sulfate, 250 mg/kg of body weight) should be instilled following emesis or lavage. Administration of the cathartic should be repeated every three to four hours until stooling has occurred. Of course, other basic supportive measures should be provided for the child as needed.

Nonproprietary Name and Trademarks of Drug

Naloxone hydrochloride—*Nalone, Narcan.*

References

1. Leach M: Naloxone: A new therapeutic and diagnostic agent for emergency use. *J Am Coll Emer Phys* 2:21-23, 1973.
2. Rumack BH, Temple A: Lomotil poisoning. *Pediatrics* 53:495-500, 1974.
3. Smith ML, Chambers TL: Overdose of Lomotil. *Br Med J* 1:176, 1978.
4. Lovejoy FH, Mitchell AA, Goldman P: Management of propoxyphene poisoning. *J Pediatr* 85:98-100, 1974.
5. Kersh ES: Treatment of propoxyphene overdose with naloxone. *Chest* 63:112-114, 1973.
6. Kallos T, Smith TC: Naloxone reversal of pentazocine-induced respiratory depression. *JAMA* 204:932, 1968.
7. Longnecker DE, Grazis PA, Eggers GWN: Naloxone for antagonism of morphine-induced respiratory depression. *Anesth Analg* 52:447-453, 1973.
8. Hasbrouck JD: The antagonism of morphine anesthesia by naloxone. *Anesth Analg* 50:954-959, 1971.
9. Shaul WL, Wandell M, Robertson WD: Dextromethorphan toxicity: Reversal by naloxone. *Pediatrics* 59:117-119, 1977.
10. Foldes FF, Duncalf D, Kuwabara S: The respiratory, circulatory, and narcotic antagonistic effects of nalorphine, levallorphan and naloxone in anaesthetized subjects. *Can Anaesth Soc J* 16:151-161, 1969.
11. Sandoval RG, Wang RIH: Narcotics and narcotic antagonists in clinical practice. *Drug Therapy* 1:41-52, 1971.
12. Jasinski DR, Martin WR, Haertzen CA: Human pharmocology and abuse potential of Nallylnoroxymorphone (naloxone). *J Pharmacol Exp Ther* 157:420-426, 1967.
13. Mitchell AA, Lovejoy FH, Goldman P: Drug ingestions associated with miosis in comatose children. *J Pediatr* 89:303, 1976.
14. *Physician's Desk Reference,* ed 32. Oradel, NJ, Medical Economics Co, Litton Industries Inc, 1978.
15. Snyder SH, Pert CB, Pasternak GW: The opiate receptor. *Ann Intern Med* 81:534-540, 1974.
16. Snyder SH: Opiate receptors in the brain. *N Engl J Med* 296:226-271, 1977.
17. Martin WR: Naloxone. *Ann Intern Med* 85:765-768, 1976.
18. Evans LE, Swainson PC, Roscoe P, et al: Treatment of drug overdose with naloxone, a specific narcotic antagonist. *Lancet* 1:452-455, 1973.
19. Pert CB, Pasternak GW, Snyder SH: Opiate agonists and antagonists discriminated by receptor binding in brain. *Science* 182:1359-1361, 1973.
20. Michaelis LL, Hickey PR, Clark TA, et al: Ventricular irritability associated with the use of naloxone hydrochloride. *Ann Thorac Surg* 18:608-614, 1974.
21. Tanaka G: Hypertensive reaction to naloxone. *JAMA* 228:25-56, 1974.
22. Eckenhoff JE, Elder JD, King BD: N-allyl-normorphine in the treatment of morphine or demerol narcosis. *Am J Med Sci* 223:191-197, 1952.
23. Wikler A, Havelock FF, Isbell H: N-allyl-normorphine: Effect of single doses and precipitation of acute "abstinence syndromes" during addiction to morphine, methadone, or heroin in man. *J Pharmacol Exp Ther* 109:8-20, 1953.
24. Freye E: Cardiovascular effects of high dosage of fentanyl, meperidine, and naloxone in dogs. *Anesth Analg* 53:40-47, 1974.
25. Weinstein SH, Pfeffer M, Schor JM, et al: Absorption and distribution of naloxone in rats after oral and intravenous administration. *J Pharm Sci* 62:1416-1419, 1973.

60 YEARS AGO IN THE AJDC

The Elimination of Acetone Bodies During Infectious Fevers

The elimination of acetone bodies (acetone, diacetic acid and beta-hydroxy butyric acid) has been documented previously during the course of some infectious diseases. Quantitative studies, especially as related to the type and degree of sickness with specific illnesses, have not been studied. The normal child eliminates 20 to 100 mg daily. Forty-one children who had scarlet fever, diphtheria, measles and pneumonia were studied. Of these only twenty-four showed acetone excretion above normal levels; in some of these the amount was only slightly elevated over normal.

There appeared to be no correlation of acetone found with the type of illness, the height or duration of the fever or the extent of prostration of the child. Some who excreted large amounts were not remarkably ill. The decrease in food intake, a consistent part of infectious diseases, did not appear to be an important or consistent relationship.—Borden S. Veeder, MD, Meredith R. Johnston, MD, Capt USA, Washington University School of Medicine, St Louis (19:141, February 1920).

Infectious Mononucleosis Initially Seen as Cold-Induced Acrocyanosis

Association With Auto-Anti-M and Anti-I Antibodies

Joseph D. Dickerman, MD; Philip Howard, MD; Sarah Dopp, MT (ASCP); Richard Staley, MD

• A case of infectious mononucleosis initially seen as cold-induced acrocyanosis is discussed. Serological evaluation of the patient showed the presence of auto-anti-M and anti-I antibodies. Both the M and I antigens are normally found on RBCs. It is postulated that one or both of these antibodies were responsible for the acrocyanosis.

(*Am J Dis Child* 134:159-160, 1980)

Infectious mononucleosis is a disease that can have a variety of signs and symptoms.[1,2] A case of infectious mononucleosis was initially seen as cold-induced acrocyanosis. To the best of our knowledge, this is the first report of such a clinical presentation.

Serological evaluation of the patient showed the presence of cold agglutinating anti-I and auto-anti-M antibodies. The I antigen is normally present on most adult RBCs. The M antigen is present on the RBCs of about 75% of all people. We are unaware of other cases of infectious mononucleosis where the presence of an auto-anti-M antibody has been demonstrated.

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REPORT OF A CASE

In August 1975, a 5-year-old boy was admitted to the Medical Center Hospital of Vermont, Burlington, with a three-day history of swollen lymph nodes, left earache, and mild sore throat. He had received oral penicillin G potassium for the last two days. Three days prior to admission, the patient's mother noted that his tongue turned blue after he had eaten vanilla ice cream. On several occasions over the next two to three days, the patient's nose, lips, fingers, and toes were noted to turn blue. These episodes lasted for a few minutes and were usually relieved by warming the child. The blue toes were noted particularly after the child played on linoleum or on a hardwood floor early in the morning, and the toes returned to their normal color once the patient was removed from the floor. There was no previous history of cardiac or pulmonary disease and no previous history of cyanosis or intolerance to cold. Results of physical examination were essentially within normal limits except for the following: he appeared mildly ill; his temperature was 37 °C; the pharynx was inflamed, with severely enlarged tonsils that were coated with large patches of a white, cheesy exudate; there were large, tender anterior cervical lymph nodes and some nontender posterior cervical lymph nodes; and, the spleen was palpated 4.5 cm below the left costal margin. No clubbing, icterus, or cyanosis was noted. Several attempts to obtain blood by a finger-stick technique resulted in instantaneous clotting in the small capillary tubes. A small sample of blood was obtained by venipuncture and placed in a refrigerator. After ten minutes, severe agglutination of the RBCs was noted. This agglutination was reversible by hand-warming the sample.

The hematocrit level was 37%, and the hemoglobin level was 12.0 g/dL. The WBC count was 13,000/cu mm, with 21% segmented neutrophils, 6% band forms, 70% lymphocytes, and 3% monocytes. Many of the lymphocytes were atypical in appearance. The RBCs and platelets appeared clumped on the peripheral blood smear. A throat culture was negative for group A streptococci. A slide test for heterophil antibody of infectious mononucleosis was strongly positive on two occasions. The results of urinalysis were within normal limits, except for a moderate amount of ketones. The platelet count was 300,000/cu mm, the reticulocyte count was 1.2%, and the prothrombin time was 11 s, with a control of 11.8 s. The partial thromboplastin time was 31 s, with a control of 30 s. The venous clotting time was seven minutes (normal, <15 minutes). The fibrinogen level was 268 mg/dL (normal, 190 to 440 mg/dL), and a cold agglutinin titer was positive at 1:1,024 dilution. An ox-cell hemolysin titer was positive at 1:640 dilution.

The patient was typed as blood group A_1 and his RBCs were agglutinated by all of

four different anti-M typing sera. The direct Coombs' reaction was initially positive. During the clinical illness, his serum was found to contain both anti-M and anti-I antibodies, with much stronger reactions occurring at lower temperatures (anti-M titer 1:1,024, anti-I titer 1:512 at 4 °C), although weaker reactions could be observed at body temperature (anti-M titer 1:64 and anti-I titer 1:16 at 37 °C). The patient's own M-positive RBCs were agglutinated by his serum and absorbed anti-M from the serum at low temperatures. The anti-M could be recovered subsequently by elution of the cells.

Serum obtained six months after cessation of clinical mononucleosis continued to demonstrate the presence of anti-M and anti-I antibodies, but reactions were limited to temperatures of 18 °C or below. The direct Coombs' reaction was now negative.

Because the history suggested cold-induced cyanosis, the patient was given orange-flavored ice sticks on several occasions. After sucking it, the patient's tongue became dark blue, but quickly reverted to its normal pink following withdrawal of the ice stick. Having the patient immerse his hands and feet in ice water produced no change in skin color. One month after discharge, the patient was playing outside in the early evening when his mother noted that his nose had turned blue and that he had a bluish discoloration to his finger tips and around his mouth, which disappeared after he came into the house. Two months after discharge, the patient was seen by his private physician, who noted that the patient's fingers turned blue after he had played on a tiled floor in the office. Since this last episode, the patient has had no other similar occurrences and has been in excellent health.

COMMENT

It has been noted that infectious mononucleosis is unique in the number of diverse antibodies that accompany the disease.[3] The antibody response in infectious mononucleosis includes not only heterophil and Epstein-Barr virus antibodies, but also Donath-Landsteiner cold hemolysins, lymphocytotoxins, anti-T and B-cell antibodies, and smooth-muscle antibodies.[4] In addition, antibodies have been found against human thyroid tissue and rat hepatocytes.[5] The most common antibody with blood group specificity found in infectious mononucleosis is anti-i, which may be present in up to 70% of all cases,[6] although we could not demonstrate it in our patient. Hemolytic anemia is present in 1.7% to 3% of all cases of infectious mononucleosis,[2] and the anti-i antibody has been reported to be responsible for this phenomenon.[7] Hemolytic anemia has also been associated with a positive Donath-Landsteiner reaction.[8]

In one report, auto-anti-N antibody was responsible for decreased RBC survival in mononucleosis.[9] The MN blood group system is itself unusual in the high frequency of autoantibodies found in people without evidence of disease. When normal blood donors are screened using sensitive low ionic strength hexadimethrine bromide polybrene techniques, examples of both anti-N and anti-M antibodies are detected in blood donors whose RBCs contain the corresponding antigen.[10] In some of these cases, the antibody is only transiently present. A recent observation is the increased frequency of auto-anti-N antibodies in hemodialysis patients.[11]

During the acute phase of infectious mononucleosis, cold-sensitive autoantibodies have been detected in 8% to 70% of all cases.[12] Both the anti-M and anti-I antibodies in our patient react at low enough temperatures to be implicated in the acrocyanosis observed on exposure to cold. A possible mechanism for these observations is that "...as blood flows through the capillaries of the skin and subcutaneous tissue, the temperature of the blood falls to as low as 28 °C if the ambient temperature is low. If the cold antibody is active at these temperatures, it agglutinates the cells, and fixes complement. The agglutination obstructs the circulation and results in acrocyanosis.[11,13]

Six months following cessation of clinical symptoms, presence of the anti-M antibody was still easily demonstrable, although presence of the anti-I autoantibody was less clearly shown. Persistence of the acrocyanosis in this patient may have been in part related to the continued presence of the anti-M antibody. Studies were not done to prove whether the autoantibodies resulted in an actual decrease in RBC survival. However, there was no clinical or laboratory evidence that the RBC survival was impaired.

John J. Murray, MD, referred the patient.

References

1. Finch SC: Clinical symptoms and signs of infectious mononucleosis, in Carter RL, Penman HG (eds): *Infectious Mononucleosis*. Oxford, England, Blackwell Scientific Publications, 1969, pp 19-46.
2. Karzon DT: Infectious mononucleosis. *Adv Pediatr* 22:231-265, 1976.
3. Dameshek W: Speculations on the nature of infectious mononucleosis, in Carter RL, Penman HG (eds): *Infectious Mononucleosis*. Oxford, England, Balckwell Scientific Publications, 1969, pp 225-240.
4. Immunopathology of infectious mononucleosis, editorial. *Lancet* 2:712-714, 1973.
5. Sutton RNP, Emond RTD, Thomas DB, et al: The occurrence of autoantibodies in infectious mononucleosis. *Clin Exp Immunol* 17:427-436, 1974.
6. Hossaini AA: Anti-i in infectious mononucleosis. *Am J Clin Pathol* 53:198-203, 1970.
7. Walker JA, Dickenson PB: Anti-i hemolytic anemia in infectious mononucleosis. *Minn Med* 59:301-302, 1976.
8. Wishart MM, Davey MG: Infectious mononucleosis complicated by acute haemolytic anemia with a positive Donath-Landsteiner reaction. *J Clin Pathol* 26:332-334, 1973.
9. Bowman HS, March WL, Shumacher HR, et al: Auto anti-N immunohemolytic anemia in infectious mononucleosis. *Am J Clin Pathol* 61: 465-472, 1974.
10. Perrault R: Naturally-occurring anti-M and anti-N with special case: IgG anti-N in a NN donor. *Vox Sang* 24:134-149, 1973.
11. McLeish WA, Brathwaite AF, Peterson PM: Anti-N antibodies in hemodialysis patients. *Transfusion* 15:43-45, 1975.
12. Horwitz CA, Moulds J, Henle W, et al: Cold agglutinins in infectious mononucleosis and heterophil-antibody-negative mononucleosis-like syndromes. *Blood* 50:195-202,1977.
13. Pruzanski W, Shumak KH: Biologic activity of cold-reacting autoantibodies. *N Engl J Med* 297:583-589, 1977.

Accidental Ingestion of Vacor Rodenticide

The Symptoms and Sequelae in a 25-Month-Old Child

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• A recently introduced rodenticide containing N-3-pyridylmethyl N′-p-nitrophenyl urea (PNU), Vacor, was accidently ingested by a 25-month-old child, resulting in acute vomiting, lethargy, seizures, and hypoglycemia, as well as chronic evidence of autonomic and peripheral neuropathy and glucose intolerance. Treatment with niacinamide (nicotinamide), may have been of benefit since all problems were resolved within three months of ingestion. This agent (PNU) is remarkably similar chemically and toxicologically to alloxan and streptozocin, both potent beta-cell toxins. These similarities are not only important in regard to the antidote for PNU, but they also suggest that the toxin may cause long-term endocrinologic, neurologic, and oncologic problems.

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Accidental ingestion of household chemicals is a common occurrence in early childhood. This report describes the case of a child who ingested Vacor, a recently introduced rodenticide (DLP-787, 2% bait; DLP-787, 10% house mouse tracking powder), manufactured by the Rohm and Hass Company, Philadelphia. Vacor contains N-3-pyridylmethyl N′-p-nitrophenyl urea (PNU), a substance chemically related to alloxan and streptozocin.[1] Both alloxan and streptozocin are potent beta-cell toxins and have been used for a number of years to induce experimental diabetes in animals and to treat islet-cell carcinomas. Apparently, PNU has similar adverse effects on beta cells since it produces hyperglycemia in rats and diabetes mellitus in humans.[1-2-3]

Since the introduction of Vacor in 1975, reports of ingestions by adults in suicide attempts have been documented, but, to our knowledge, this is the only well-documented ingestion reported in the pediatric age group. This agent not only has substantial acute problems associated with its ingestion, but also has the potential for causing definite long-term sequelae.

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REPORT OF A CASE

A 25-month-old boy arrived at the St Paul (Minn) Children's Hospital Clinic with symptoms of vomiting, lethargy, anorexia, and a major motor seizure. The child had been in good health, except for a three-day history of rhinitis, until the night before admission when he vomited five times prior to going to bed. The next morning, his mother reported he was stuporous and anorectic and he vomited once again. Shortly thereafter, he had a major motor seizure lasting about two minutes and was brought immediately to the hospital. During the admission interview, the parents expressed concern that the child may have ingested Vacor, which they had placed around the house. The patient's cousin later admitted to feeding the child an unknown amount of the substance on a piece of gum.

The patient's medical history was unremarkable except for a seizure with fever at the age of 16 months. Metabolic and neurologic evaluations at that time showed no abnormalities. Family history showed a deceased maternal grandmother who had juvenile onset diabetes mellitus.

On admission, the patient was lethargic, inconsistently responsive, but generally arousable to vigorous stimuli. His vital signs included the following: weight, 14.9 kg; temperature, 36.2 °C; pulse rate, 104 beats per minute; respirations, 26/min; and blood pressure, 82/50 mm Hg. There was no evidence of trauma. His neck tone was normal; the cranial nerves were normal and the fundi were clear. There was a mild ptosis bilaterally and his face appeared slightly puffy. The pupils were generally constricted but dilated when the patient was aroused. Deep-tendon reflexes were symmetric but brisk, and both Babinski's signs were positive. The remainder of the results of the physical examination were within normal limits except for a mild rhinitis.

At the time of his arrival to the clinic, the seizure had stopped, and he was lethargic. He was given 90 mg (6 mg/kg) phenobarbital intramuscularly, and gastric lavage was performed immediately. A blood sample was obtained and an intravenous (IV) infusion of dextrose and an electrolyte solution was started. Niacinamide (100 mg) was given intravenously. The blood sample drawn at 10 AM, prior to the IV infusion gave the following results: blood glucose, 18 mg/dL with low serum ketones (1+); serum sodium, 145 mEq/L; potassium, 4.5 mEq/L; calcium, 5.8 mEq/L; BUN, 15 mg/dL; SGOT, 35 mU/mL; serum ammonia, 51 μg/dL; and venous pH, 7.37 with a P_{CO_2} of 37.7 torr. The complete blood cell count showed a hemoglobin level of 11.3 g/dL and a WBC count of 11,700/cu mm, with 80% neutrophils, 12% lymphocytes, and 8% monocytes. Blood lead level was 0.028 mg/dL (normal, less than 0.040 mg/dL). Tests for heavy metals showed no evidence of mercury, arsenic, antimony, or bismuth in the urine. The EEG done shortly after admission showed multifocal spikes consistent with a seizure disorder. In the hour after admission to the hospital, he continued to have noticeable fluctuation in his level of consciousness. At 2 PM, when the presence of hypoglycemia was reported, he was immediately given 20 mL of 25% dextrose solution. He showed a gradual return to a more wakeful state within the next 40 minutes and subsequently had only one further episode of unresponsiveness and fixed gaze. The blood glucose level, just prior to the dextrose infusion, was 46 mg/dL; and 1¼ hours later, it was 102 mg/dL. He was given 100 mg of niacinamide intravenously at 3 PM and again at 9 PM, at which time the blood glucose level was 255 mg/dL. Four hours later, it was 155 mg/dL.

The child had no seizures the next day. Niacinamide (50 mg) was given intravenously every four hours. The blood glucose level remained in the range of 175 mg/dL but increased to 350 mg/dL on the third day and to 380 mg/dL by the fifth day. Urinary glucose levels fluctuated from trace to 4+ with small to large acetones

initially, followed by negative urine acetone values. Serum acetone tests always remained negative.

On the third day, IV feedings were discontinued, and oral doses of 50 mg of niacinamide were given four times a day. The child had been eating, but he experienced liquid stools during that day. On the fourth day, his mother reported that he seemed to have pain. Examination showed him to be listless and fussy. When sitting up, he was unsteady and attempted to stiffen his extremities. The pain seemed to increase on movement. His eyes were watering, his respirations were noisy, and he had a poor cough. His abdomen was distended, and there was muscle guarding. His SGOT level, which had increased from 35 mU/mL on day 1 to 116 mU/mL on day 3, now was 24 mU/mL. A prothrombin time of 15.5 s (control, 12.1 s) and a partial thromboplastin time of 83 s (normal, 50 s) were reported. Serum amylase level was 169 units/dL (normal, 60 to 160 units/dL).

The next day, his abdomen was firm, tender to palpation, and tympanitic to percussion. He no longer was having loose stools but did not have control of bowel or bladder function. He had previously been toilet trained and was able to void in the urinal. Abdominal roentgenograms showed ileus. A chest roentgenogram showed a patchy pneumonitis of both lower lobes. Intravenous feedings were reinstituted, 50 mg niacinamide was administered intravenously every six hours, and 600,000 units of aqueous penicillin G potassium were given every six hours intravenously. On the eighth hospital day, his mother reported he laughed and talked for the first time since admission. However, we found him to be only slightly more alert and still lethargic and irritable. His abdomen was softer, with minimal muscle guarding.

By the 11th hospital day, he had leg pain. During examination, he resisted manipulation of both legs and refused to stand. The severity of pain seemed to vary from one leg to the other. He had not stood since the time of admission. Roentgenograms and a bone scan were done of both legs to rule out an infectious process. Both studies were normal. Electromyography of the boy was refused by the mother. Neurologic examination showed reflexes to be brisk and symmetric, with intact sensation.

The pneumonitis cleared by the 13th day. He continued to be lethargic and irritable and he was in pain. He was discharged on the 15th day and was still unable to stand or walk. At this time, he had glucosuria (3 to 4+) but no ketonuria. He was on a regular diet, and quantitative urine glucose tests done near the end of the hospital stay showed the patient to be spilling approximately 15% of the dietary carbohydrate intake. Insulin injection therapy was not given during the hospital stay nor after discharge. An EEG done on the 14th hospital day was normal. His mother was instructed to give him 50 mg of niacinamide orally every six hours to be continued for the next four weeks.

One week after discharge, the patient still seemed to be in pain. He refused to walk and would not stand without support, but would slowly move his legs. He consistently had glucosuria (3+) but no ketonuria. A single blood glucose value was 321 mg/dL. A week later, a glucose tolerance test result was normal, as were simultaneous insulin levels. The child continued to have leg pain.

Three weeks after discharge from the hospital, the patient was talking, but his gait was unsteady and wide based. His eyelids were still droopy and he had not recovered bowel or bladder control. Tests showed negative urine glucose values.

RESULTS

The patient was then lost to follow-up until he was brought to the emergency room about three months later with a grand mal seizure associated with a temperature of 41 °C. Tests showed normal blood glucose and serum electrolytes levels, and there was no evidence of glucosuria or ketonuria. When fully examined the next day, there was no evidence of leg pain or gait abnormalities. The ptosis had resolved and he had regained control of his bowel and bladder function. Niacinamide therapy had been discontinued. Further examinations have not been done though his mother reports that he seems entirely normal.

COMMENT

Toxic Effects and Clinical Symptoms

This PNU is a potent toxin that causes death or severe sequelae in a high proportion of individuals who ingest it.[1,4,5] As ingestions of rodenticides containing PNU become more frequent in children, it is imperative that physicians familiarize themselves with the symptoms caused by the toxin.

The acute clinical symptoms of intoxication seem to be vomiting, alterations in the state of consciousness with possible seizures, and disturbances in glucose homeostasis. The symptoms are similar to those associated with ingestions of other drugs such as salicylates and oral hypoglycemic agents or to the symptoms of metabolic disturbances such as diabetic ketoacidosis. These clinical and laboratory manifestations are similar to the abnormalities produced in humans and laboratory animals from the closely related compounds streptozocin and alloxan. Nausea and vomiting have been reported in up to 75% of patients for whom streptozocin was being used to treat malignant neoplasms.[6] Disturbances in blood glucose levels seem to be almost identical to the responses seen in laboratory animals given toxic doses of either drug.

Both streptozocin and alloxan produce a triphasic response after injection.[7] The first phase is a brief period (one to four hours) of hyperglycemia. The degree of hyperglycemia seems to be dependent on liver glycogen concentration and is accompanied by low circulating immunoreactive insulin (IRI) levels. The second phase is a period of severe hypoglycemia lasting up to 48 hours. Levels of IRI are notably elevated during this period, probably due to massive beta-cell necrosis and release of stored hormone. Experimental animals convulse and often die during this period. The third phase is a period of chronic hyperglycemia that may be of long, if not permanent, duration. The severity and length of this period is dependent on the number of beta cells destroyed by the drug. It has not been shown that PNU produces this triphasic response, but our patient demonstrated severe hypoglycemia followed by chronic hyperglycemia. If he had been examined immediately after ingestion, he may indeed have been hyperglycemic. Thus, patients may have a wide variation in serum glucose levels depending on the time interval between ingestion and report of the incident. The documentation of the entire triphasic response may be diagnostic of PNU intoxication, but laboratory tests at any one point during the patient's acute course may not provide a definitive diagnosis. Because of this, it is imperative that PNU ingestion be considered when any child has vomiting, alterations in consciousness, and aberrations in glucose homeostasis.

In addition to the chronic diabetes mellitus of variable duration, PNU

has also been reported to cause autonomic dysfunction in the form of hypothermia, hypotension, dysphagia, dystonia, and bowel and bladder dysfunction. Motor and sensory neuropathies, and possible inappropriate antidiuretic hormone secretion are also described.[1-5] In our patient, the neurotoxic effects of PNU led to ileus, hypotonia, ptosis, mild facial paresis, and painful paresthesias. The paresthesias and fecal retention noted in our patient persisted for several weeks.

Effects on additional organ systems have not been reported in humans, but both streptozocin and alloxan have been reported to be nephrotoxic. Streptozocin has been shown to cause varying degrees of renal dysfunction such as Fanconi's syndrome, azotemia, and even anuria after treatment.[6-8-9] Alloxan is known to produce similar transient effects in animals.[10] There is also evidence that both drugs in high doses cause liver damage. Streptozocin has been reported to cause damage to the exocrine pancreas, leukopenia, and thrombocytopenia.[6-11-12] This may explain the transient, mild increase in both serum transaminase and amylase levels noted in our patient.

Mechanism of PNU Toxicity

The exact mechanism of PNU toxicity is not known, but preliminary evidence indicates niacinamide antagonism.[2] It seems to work in a manner similar to streptozocin. Streptozocin (glycopyranose, 2-deoxy-2 (3-methyl-3-nitro soureido)-D-) has been shown to exhibit antibiotic,[13] oncolytic,[6] and oncogenic[14] activity in addition to its diabetogenic potential.[15] In animals given toxic doses of streptozocin, examination of the beta cells by electron microscopy showed dilated endoplasmic reticulum, swollen mitochondria, and partial or complete degranulation of the cells.[16-17] Schein et al[16] and Schein and Loftus[18] have shown that this effect is probably mediated through the drug's specific effect on reducing intracellular synthesis of NAD and NADH (oxidized and reduced niacinamide adenine dinucleotide). One IV dose produces a 24-hour depression of both NAD and NADH concentrations in rat liver, with a return to normal concentrations by 48 hours. This effect on NAD and NADH, as well as on beta-cell ultrastructure, could be prevented by the injection of 500 mg/kg of niacinamide intraperitoneally (IP) ten minutes prior to the treatment with streptozocin. Niacinamide also seems to prevent the development of diabetes. Small serial administrations of niacinamide either IP or orally during a 24-hour period seemed to be more beneficial than a single intraperitoneal injection. This probably relates to the fact that detectable levels of streptozocin remain in rat liver for 20 hours after a single injection[18] whereas detectable niacinamide levels are only present in rodent liver for approximately 16 hours after a single intraperitoneal dose.[19]

Niacinamide seems to be the specific antagonist of choice for dealing with the effects of streptozocin. N'-methyl niacinamide, niacin (nicotinic acid), and L-tryptophan, all precursors of NAD, have no effect on either preventing streptozocin-induced depression of liver nucleotide levels or preventing the development of diabetes mellitus.[16-20] The cause for this specific effect was investigated by Tjalve and Wilander,[20] who determined that there is a relationship between the ability of the NAD precursors to be taken up by the pancreatic islets and their ability to prevent streptozocin diabetes. They found that only niacinamide was accumulated to any extent within the islet whereas L-tryptophan and niacin were not.

Other than the antagonism of PNU by niacinamide, and preliminary indications that biotransformation is important in its detoxification,[2] little is known regarding its pharmacology in animals and no data are available in humans. More is known about streptozocin,[21-22] though the pharmacology of the two drugs may not be directly comparable despite their chemical similarities.

When streptozocin (1.5 g/kg) is given by IV bolus injection, the pharmacokinetics fit a two-compartment model with the central compartment having a volume compatible with the plasma and RBC volume, and the peripheral compartment corresponding to the volume of the extracellular fluid. There is a rapid transfer to the peripheral compartment from the central compartment, but there is little in the reverse direction. The biologic half-life of the drug is 40 minutes, both in serum and tissue. The precise metabolism of streptozocin has not yet been completely determined, but the drug has several metabolites, some of which remain in tissue for several days. Urinary excretion of streptozocin or its metabolites is low (11% to 15%). Most is excreted within the first six hours after IV injection.

Treatment Regimen

The scarcity of concrete data on the pharmacology of PNU in humans makes recommendation of a dogmatic treatment regimen impossible. Emesis is recommended if the ingestion is recent enough to expect the chemical to still be in the stomach. The advisability of activated charcoal and/or cathartic administration has not been studied, but it is recommended on an empiric basis. There are no data to suggest that ion trapping and forced diuresis are of benefit. No data exist to suggest that dialysis or hemoperfusion are efficacious in treating PNU ingestions.

Niacinamide seems to be the most specific antidote for PNU ingestion. Niacinamide has been used as an antidote in rats given toxic doses of PNU.[2] It was most effective when given within one hour of ingestion. Niacin did not seem to be as effective in preventing toxicity, but rats fed high levels of L-tryptophan in their diets did seem to be protected. There is also evidence that niacinamide antagonism may play a role in the development of neurologic symptoms.[23]

With the data presently in the literature, it is impossible to predict the likelihood of permanent damage caused by PNU since dosage, age, and interval between ingestion and treatment have varied so greatly among affected individuals. Therefore, it would not be prudent to withhold treatment until the development of clinical symptoms or laboratory evidence of PNU toxicity, since permanent damage can occur by that time. We believe strongly that all individuals whose conditions are suggestive of PNU ingestion should immediately be started on a regimen of niacinamide in view of the low toxicity and potential benefit from this compound. The

recommended dosage is 50 to 100 mg niacinamide intravenously every six hours for two to three days, followed by the same dosage of niacinamide taken orally for two to four weeks.

Long-term sequelae in the form of glucose intolerance and/or neurologic dysfunction have been frequent among the survivors of acute intoxication.[1,3,5] Some individuals will have permanent insulin-dependent diabetes and others will have no carbohydrate intolerance at all. Another group, however, may have an intermediate course as our patient did, having an acute episode of hyperglycemia followed by total resolution. These individuals obviously have sustained damage to their beta cells as demonstrated by their hyperglycemia. This situation is not unlike juvenile onset diabetics who begin with an active, insulin-deficient state that improves transiently only to gradually deteriorate as residual beta-cell function is lost. These individuals who seem to have recovered may eventually lose their remaining beta-cell function and experience true insulin-dependent diabetes. Close follow-up of these individuals is obviously necessary.

Even more ominous than the specter of chronic diabetes mellitus is the possibility that PNU may share the oncogenic potential of streptozocin. Streptozocin is closely related to the carcinogenic nitrosoamines and, as such, has been reported to cause renal neoplasms in a high percentage of treated animals.[14] Rakieten et al,[24] in studying the ability of niacinamide to prevent the development of these tumors, found a decrease from 77% to 18% of tumor-positive animals when the animals were treated with niacinamide both before and three hours after their dose of streptozocin.

Treatment with niacinamide, at least in rats, does not seem to be completely without risk. Although treatment seems to prevent the development of acute symptoms and decreases substantially the incidence of renal tumors, niacinamide acts as a cocarcinogen in producing islet cell adenomas. These tumors occur in extremely high proportions of treated animals,[25-27] after a rather lengthy latent period of 19 to 24 months. Rats bearing these tumors, that seem to be benign, well-encapsulated adenomas,[28] experience and often die with profound hypoglycemia.

Schoental[29] has described similar tumors in rats given heliotrine, a monoester pyrrolizidine alkaloid, and niacinamide. Heliotrine apparently exerts its toxic effect in a manner similar to streptozocin by interfering with intracellular NAD levels.[30,31] Schoental's work suggested that pretreatment with niacinamide lessened some of the drug-caused damage to the liver but seemed to induce islet-cell tumors in 50% of the long-term survivors. In addition, a transitional cell papilloma of the bladder, a hepatoma, and an interstitial-cell testicular tumor were found in treated animals.

It is obviously difficult to compare the precise oncogenic potential of compounds, even if they are closely related. Similar effects of PNU may not be observed, and even if the drug is carcinogenic in humans, the affected organs may be different. Evidence is compelling, however, that in certain rat neoplasms, common metabolic pathways involving NAD metabolism may be involved in both the acute toxic effects and the delayed oncogenic sequelae; these are the same metabolic pathways that PNU seems to affect. Close follow-up observation of affected individuals is obviously indicated.

References

1. Prosser PR, Karam JH: Diabetes mellitus following rodenticide ingestion in man. *JAMA* 239:1148-1150, 1978.
2. Deckert FW, Moss JN, Sambuca AS, et al: Nutritional and drug interactions with Vacor rodenticide in rats, abstracted. *Fed Proc* 36:990, 1977.
3. Karam JH, Prosser PR, LeWitt PA: Islet-cell surface antibodies in a patient with diabetes mellitus after rodenticide ingestion. *N Engl J Med* 299:1191, 1978.
4. Rodenticide blamed for Korean deaths. *Chem Engl News* 53:8, 1975.
5. Miller LV, Stokes JD, Silipat C: Diabetes mellitus and autonomic dysfunction after Vacor ingestion. *Diabetes Care* 1:73-76, 1978.
6. Stolinsky DC, Sadoff L, Braunwald J, et al: Streptozotocin in the treatment of cancer: Phase II study. *Cancer* 30:61-67, 1972.
7. Rerup CC: Drugs producing diabetes through damage of insulin secreting cells. *Pharm Rev* 22:485-518, 1970.
8. Loftus L, Cuppage FE, Hoogstranten B: Clinical and pathologic effects of streptozotocin. *J Lab Clin Med* 84:407-413, 1974.
9. Sadoff L: Neprotoxicity of streptozotocin. *Cancer Chemother Rep* 54:457-459, 1970.
10. Lazarow A, Palay SL: The production and course of alloxan diabetes in the rat. *J Lab Clin Med* 31:1004-1015, 1946.
11. Arison RN, Ciaccio EI, Glitzer MS, et al: Light and electron microscopy of lesions in rats rendered diabetic with streptozotocin. *Diabetes* 16:51-56, 1967.
12. Junod A, Lambert AE, Orci L, et al: Studies of the diabetogenic action of streptozotocin. *Proc Soc Exp Biol Med* 126:201-205, 1967.
13. Herr RR, Eble TE, Bergy ME, et al: Isolation and characterization of streptozotocin, in Marti-Ibanez F (ed): *Antibiotics Annual. Seventh Annual Symposium on Antibiotics.* New York, Antibiotic, 1960, pp 236-240.
14. Rakieten N, Gordon BS, Cooney DA, et al: Renal tumorigenic action of streptozotocin (NSC-85998) in rats. *Cancer Chemother Rep* 52:563-567, 1968.
15. Rakieten N, Rakieten ML, Nadkarni MV: Studies on the diabetogenic action of streptozotocin. *Cancer Chemother Rep* 29:91-98, 1963.
16. Schein PS, Cooney DA, Vernon ML: The use of nicotinamide to modify the toxicity of streptozotocin diabetes without loss of antitumor activity. *Cancer Res* 27:2324-2332, 1967.
17. Lazarus SS, Shapiro SH: Serial morphologic changes in rabbit pancreatic islet cells after streptozotocin. *Lab Invest* 27:174-183, 1972.
18. Schein PS, Loftus L: Streptozotocin depression in mouse liver pyridine nucleotides. *Cancer Res* 28:1501-1506, 1968.
19. Petrack B, Greengard P, Kalinsky H: On the relative efficacy of nicotinamide and nicotinic acid as precursors of nicotinamide adenine dinucleotides. *J Biol Chem* 241:2367-2372, 1966.
20. Tjalve H, Wilander E: The uptake in the pancreatic islets of nicotinamide, nicotinic acid, and tryptophan and their ability to prevent streptozotocin diabetes in mice. *Acta Endocrinol* 83:357-364, 1976.
21. Adolphe AB, Glasofer ED, Troefel WM, et al: Fate of streptozotocin (NSC-85998) in patients with advanced cancer. *Cancer Chemother Rep* (pt 1) 59:547-556, 1975.
22. Adolphe AB, Glasofer ED, Troefel WM, et al: Preliminary pharmokinetics of streptozotocin, an antineoplastic antibiotic. *J Clin Pharmacol* 17:379-388, 1977.
23. Herken H: Antimetabolic action of 6-amino-nicotinamide on the pentose phosphate pathway in the brain, in Aldridge WN (ed): *Mechanism of Toxicity.* London, Macmillan & Co Ltd, 1971, pp 189-199.
24. Rakieten N, Gordon BS, Beaty A, et al: Modification of renal tumorigenic effect of streptozotocin by nicotinamide: Spontaneous reversibility of streptozotocin diabetes. *Proc Soc Exp Biol Med* 151:356-361, 1976.
25. Rakieten N, Gordon BS, Beaty A, et al: Pancreatic islet cell tumors produced by the combined action of streptozotocin and nicotinamide. *Proc Soc Exp Biol Med* 137:280-283, 1971.
26. Dixit PK, Bauer GE: Studies on rats with islet B-cell tumors induced by nicotinamide and streptozotocin. *Proc Soc Exp Biol Med* 152:232-236, 1975.
27. Chan SJ, Labrecque DA, Hofmann C, et al: Studies of insulin biosynthesis in streptozotocin and radiation induced B-cell tumors from rat pancreas, abstracted. *Diabetes* 25(suppl 1):343, 1976.
28. Volk BW, Wellman KF, Brancato P: Fine structure of rat islet cell tumors induced by streptozotocin and nicotinamide. *Diabetologia* 10:37-44, 1973.
29. Schoental R: Pancreatic islet-cell and other tumors in rats given heliotrine, a monoester pyrrolizidine alkaloid, and nicotinamide. *Cancer Res* 35:2020-2024, 1975.
30. Christie GS, LePage RN: Liver damage in acute heliotrine poisoning: 1. The intracellular distribution of pyridine nucleotides. *Biochem J* 84:25-38, 1962.
31. Christie GS, LePage RN: Liver damage in acute heliotrine poisoning: 2. The effect of nicotinamide on pyridine nucleotide concentrations. *Biochem J* 84:202-212, 1962.

Rothmund-Thomson Syndrome With Severe Dwarfism

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• Two patients had severe dwarfism and limb anomalies, but also had other clinical characteristics of the Rothmund-Thomson syndrome, including characteristic skin changes, abnormal hair growth, sensitivity to sunlight, defective nails and teeth, and juvenile cataracts. We emphasize that this diagnosis should be considered in any patient with extremely short stature, associated skeletal anomalies, and an early onset of typical cutaneous changes.

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Rothmund-Thomson syndrome, or poikiloderma congenitale, is a rare autosomal recessive disorder characterized by the infantile onset of dermal atrophy associated with telangiectasia, hyperpigmentation, and depigmentation. Additional findings are sparse hair or alopecia, sensitivity to sunlight, dystrophic nails, and defective dentition. More than 50% of the patients have juvenile cataracts, small hands, hypogonadism, and short stature. Congenital skeletal anomalies, primarily of the forearms and hands, are less common, but they have been observed in about 5% of the reported cases. We describe two patients with severely short stature, limb anomalies, and other clinical findings suggestive of the Rothmund-Thomson syndrome. These patients illustrate that in some cases features that are usually considered minor may predominate over the dermatologic manifestations.

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REPORT OF CASES

CASE 1.—This infant (Fig 1) weighed 1.6 kg and was 40 cm long at birth. She was delivered by breech after a 36-week gestation to a 29-year-old gravida 4 , para 4, abortus-0 mother and a 37-year-old unrelated father. There was no family history of congenital anomalies, abortions, stillbirths, or neonatal deaths. She required hospitalization for three months after birth for feeding difficulties, but had no respiratory problems. Skeletal abnormalities noted at birth were bilateral absence of the first metacarpal and thumb and absence of the left radius and hypoplasia of the right radius, which resulted in the radial deviation of both hands. The other fingers were normal, but there was shortening of the first toes bilaterally. Postnatal growth was poor, and she weighed only 3.2 kg at 7 months of age. She had a striking craniofacial disproportion with absence of the supraorbital ridges and a large anterior fontanelle, which suggested hydrocephalus

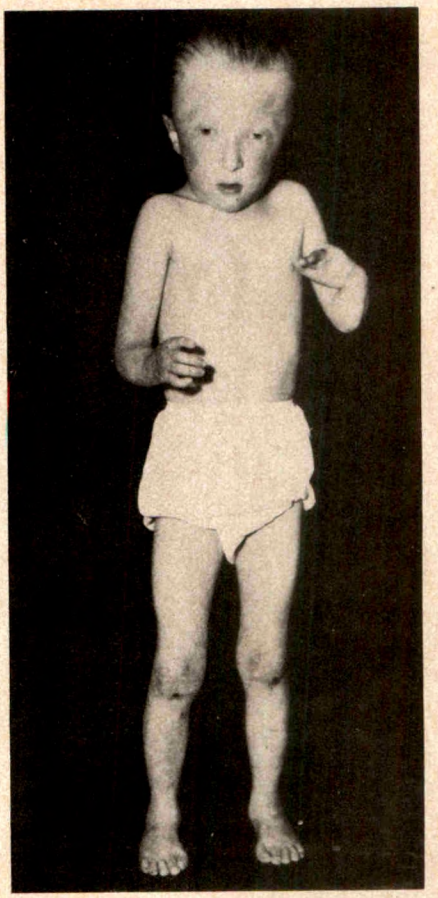

Fig 1.—Patient 1 at age 5 years, 11 months. Typical cutaneous changes with dermal atrophy and hyperpigmentation are present on face and extensor surfaces of limbs. Absence of thumbs and left radius and hypoplasia of right radius are seen.

to some observers. Many other "soft spots" were present on the patient's head, apparently representative of areas of thin calvaria.

Freckles over her trunk, limbs, and face were present at birth. The freckles were exacerbated by the sun at about 1 year of age, and redness, telangiectasia, and atrophic areas appeared later. Sweating was normal. Sun-exposed skin tanned normally despite a tendency to sunburn. Eyebrows and eyelashes were absent from birth. Fingernails and toenails tended to grow slowly. At age 7 years, several carious teeth were extracted. Menarche was at age 12 years, with normal secondary sexual development. She was of normal intelligence and graduated from high school at the usual age with average grades.

Despite the limb anomalies, she had no orthopedic problems until 7 years of age, at which time her feet and knees appeared internally rotated. Roentgenograms showed bilateral absence of the patella, a straight spine, and metatarsus adductus with apparent talocalcaneal fusion and talonavicular fusion on the right. The distal femoral and proximal tibial epiphyses were abnormal, and there was lateral displacement of the tibiae with a mild valgus deformity of the knees and bilateral posterior subluxation of the proximal tibia. The femoral heads and hips were normal. Bilateral supracondylar femoral osteotomies performed at age 9 years failed to correct the flexion and valgus deformities, and osteoporosis of the long bones of the leg subsequently occurred. At age 15 years, she had a Charnley compression arthrodesis of the left knee to fuse the joint and correct the residual flexion deformity and posterior subluxation of the tibia.

The patient was first examined by us at age 19 years. Her height was 113.8 cm, her weight was 24.5 kg, and her occipitofrontal circumference was 44.8 cm. Extensive skin involvement included a "freckled" appearance over most of the body that was interspersed with areas of atrophy and hypopigmentation with telangiectasia predominantly over extensor surfaces of her limbs. Her facies was distinctive (Fig 2) with a high, flat forehead, a lack of supraorbital ridges, and a long, thin, prominent nose. Despite a history of normal scalp-hair growth, the hair was thin in places, and her eyebrows and lashes were completely absent; her eyes were normal. Her mouth was small, and the teeth were carious. The mandible was small and receding. Skeletal changes included bilateral absence of the

Fig 2.—Patient 1. Characteristic facies includes high forehead, lack of supraorbital ridges, long nose, and sparse eyebrows and eyelashes.

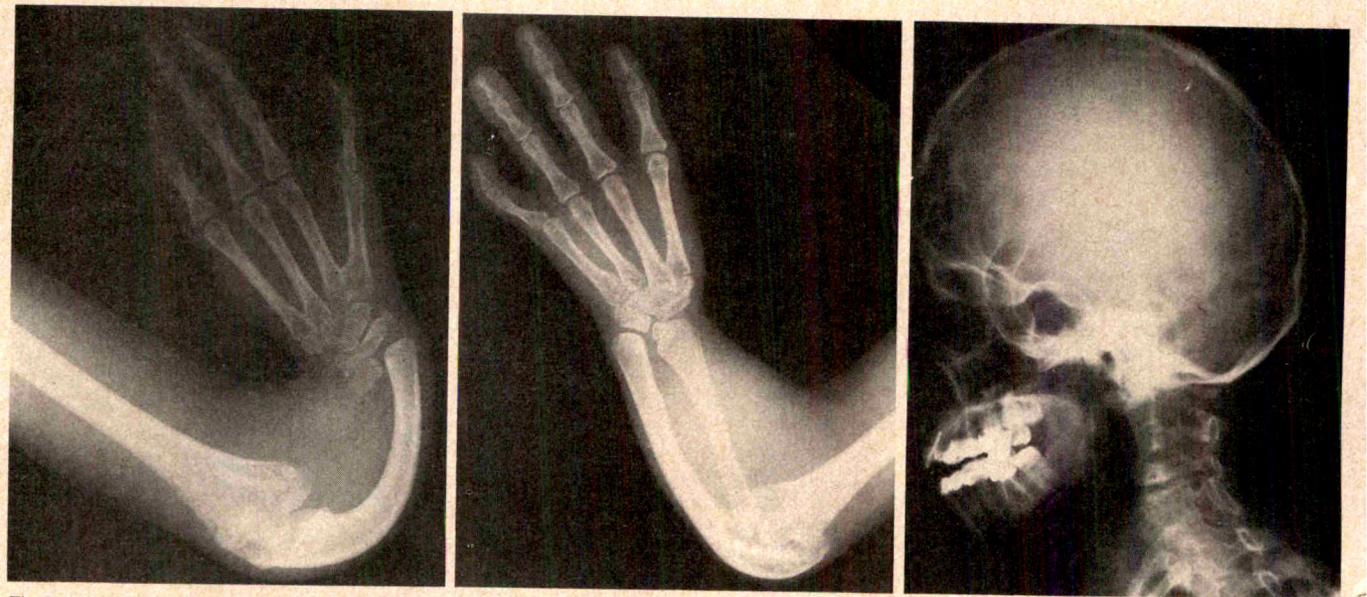

Fig 3.—Patient 1 at 19 years of age. Left and Center, Note bilateral absence of first metacarpal and thumb, small second and fifth middle phalanges, fusion of fourth and fifth metacarpals on left, absence of left radius, and hypoplasia of right radius. Right, Skull appears microcephalic, with increased markings and flat angle at base. Cervical vertebrae are irregular and fused.

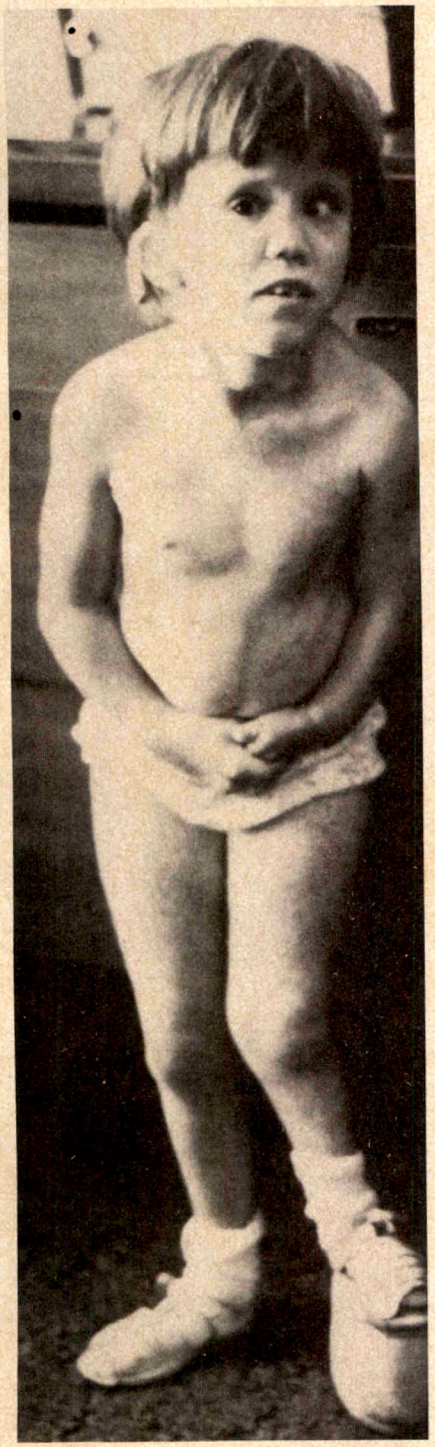

Fig 4.—Patient 2 at 11 years of age. Note proportionate short stature with radial hypoplasia and short leg on left, small nose, strabismus, asymmetric chest, and irregular areas of dark pigment.

Fig 5.—Patient 2 has dermatologic changes with irregular pigment and areas of hypoplastic skin.

first metacarpal and thumb, absence of the left radius, and hypoplasia of the right radius (Fig 3). The femur was displaced medially. The fibula and tibia had narrow diaphyses. Her skull appeared microcephalic, with increased markings and a flat angle at the base. The cervical vertebrae were irregular and fused (Fig 3). The lumbar vertebrae were relatively tall and tubular, with mild irregularities and narrow disk space. Increased lumbar lordosis was present.

CASE 2.—A female infant (Fig 4) was born at term weight, 2.2 kg, length, 43.8 cm, the product of the first pregnancy of 25-year-old unrelated parents. The mother was 168.8 cm tall, and the father was 190.0 cm tall. Prior to pregnancy, the mother had erythema nodosum that continued into the first trimester. In addition, the mother had a tonsillectomy under general anesthesia during the first month of pregnancy. After the operation, she received oral doses of codeine for one to two weeks.

At birth, the patient was noted to have a saddle nose and bilateral cataracts. She had multiple tiny hemangiomata over her face, trunk, buttocks, extremities, and one palm; her skin was otherwise normal, and the hemangiomata disappeared during the first year of life. Freckles and cafe-au-lait spots began to appear at age 4 years without preceding erythema or sun sensitivity. There was no history of blistering, but atrophic areas of skin gradually appeared.

Roentgenograms at 3 months of age reportedly showed deformities of the vertebrae and shortening of the metacarpals and metatarsals, fibula, and radius. At 5 months of age, asymmetric disproportionately short stature with shortening of the left leg and left arm with bilateral asymmetric brachydactyly was noted. Epiphyses were mottled and irregular, and the diagnosis of Conradi-Hünermann syndrome was considered, but no stippling of the epiphyses was seen at that time or on roentgenograms obtained at 1 year of age. Shortening in the left leg was primarily accounted for by the tibia, and the second, third, and fourth toes were asymmetrically short. Asymmetry of leg length required shoe lifts from age 3 years. At age 6 years, kyphoscoliosis of the thoracic spine was treated with a Milwaukee brace.

Cataracts were surgically extracted at 8 months of age; the remainder of the findings of her eye examination were normal, except for strabismus. At 2½ years of age she was found to have sensorineural deafness of moderate severity, a 60- to 80-dB loss bilaterally. During early infancy, she occasionally had lingering chest colds, but otherwise was healthy throughout childhood.

She had a severe growth deficiency: a height of 53.8 cm and weight of 4.1 kg at 4 months of age, 63.8 cm and 6.8 kg at 2½ years, and 72.5 cm and 7.3 kg at 5½ years. Tooth eruption was delayed so that at age 15 months she had only three teeth.

Motor development was delayed; she neither sat nor pulled herself to a standing position until after 1 year of age; she pulled herself to a standing position by 3 years of age, but was walking only poorly at 5 years of age. At age 9 years she was in special education classes, but was functioning at an age-appropriate level in many areas.

On physical examination at 9 years of age she was 82.5 cm tall and had patchy depigmentation and areas of marbled hyperpigmentation on her trunk (Fig 5). Patches of dry and atrophic skin were intermixed with hyperpigmented macules on the extensor surface of the arms and legs. Except for patches of alopecia, the scalp hair showed normal growth and texture. Eyebrows were sparse, but the eyelashes were normal. She had frontal bossing, a prominent venous pattern of the forehead, and midface hypoplasia with a flattened nasal bridge and upturned nasal tip. The mandible was small. The primary teeth were dysplastic, with only one

secondary tooth present. Her teeth were widely spaced and irregular. Her voice has always been high pitched, with a squeaky quality. Her ears were small and thickened.

The left leg was 8 cm shorter than the right, with marked bilateral genu valgum. There was decreased extension of both elbows; her right arm appeared to be normal, but her left radius was hypoplastic, and the hand was radially deviated. Kyphosis of 90° in the upper thoracic spine was combined with a moderate degree of scoliosis.

When seen again at 11 years of age (Fig 4), she was 90.0 cm tall and weighed 11.4 kg. Her head was at less than the third percentile for her age (occipitofrontal circumference, 47.5 cm), although it appeared proportionate for her height. Except for several graying scalp hairs, there was no significant change in the findings of her physical examination. Chromosome studies with R-banding from peripheral blood and a skin fibroblast culture were 46, XX without breaks, gaps, or marker chromosomes detectable; 180 metaphases were studied.

No relatives are similarly affected; however, the patient's mother and maternal grandmother both have angiokeratoma corporis diffusum that developed during pregnancy. Neither of them has other pigmentary problems. The patient's only sibling, a brother, is unaffected and healthy.

Characteristic Abnormalities of Rothmund-Thomson Syndrome

Feature	Frequency of Occurrence,* % (No.)	Presence	
		Case 1	Case 2
Skin changes: atrophy, erythema, pigmentation, telangiectasia	100 (46)	Yes	Yes
Female	72 (33)	Yes	Yes
Short stature	54 (25)	Yes	Yes
Juvenile cataracts	52 (24)	No	Yes
Sparse or absent eyebrows and eyelashes	50 (23)	Yes	Yes
Skeletal anomalies	39 (18)	Yes	Yes
Skin sensitive to sunlight	35 (16)	Yes	No
Hypogonadism	24 (11)	No	No†
Dystrophic nails	24 (11)	Yes	No
Defective dentition	15 (7)	Yes	Yes

*Indicates that the percentages are from 46 cases reviewed by Taylor[6] in 1957.
†Indicates that the patient is prepubertal.

COMMENT

Rothmund-Thomson syndrome is a rare autosomal recessive disorder that was first described by Rothmund[1] in 1868 as an association of "cataracts. . .with a peculiar skin degeneration" and later by Thomson in 1923[2] and 1936[3] as poikiloderma congenitale (literally, "congenital variable skin"). Its clinical characteristics vary greatly, but the major features are the characteristic dermatologic findings often associated with cataracts, short stature, hypogonadism, skeletal anomalies, and typical facies (Table 1).

The skin changes are summarized by Rook et al.[4] They emphasize that the first dermal manifestations typically appear between 3 and 6 months of age, but occasionally are present at birth or appear as late as 2 years of age. The initial lesions are usually erythematous plaques, reticular erythema, or diffuse erythema of the face (especially the cheeks), with gradual involvement of the dorsum of the hands and forearms and the extensor surfaces of the legs, thighs, and buttocks by the end of the second year. Sun-exposed skin is typically more severely involved, while the trunk and flexor aspects of the limbs are usually spared. The palms are never involved. Sun sensitivity, which was seen in all cases, often causes bullous eruptions with minimal exposure and diminishes with age.

The erythematous stage is followed by the chronic poikilodermatous stage, which consists of dermal atrophy, telangiectasia, depigmentation, and hyperpigmentation in a characteristic distribution over the extensor surfaces of limbs. Typically, multiple small, pale, atrophic circumscribed macules are enclosed by a reticulate pattern of dull red telangiectasias. "Smudges" of brown pigmentation develop later in the areas of atrophy and telangiectasias and may extend over uninvolved skin, especially on the neck and trunk. Macular areas of depigmentation without atrophy are also seen. In general, the telangiectasias predominate on the face and hands, while the pigmentary changes involve the limbs and trunk, where they may be the only abnormality. Xerodermatous scaling of the skin of the extremities occurs in time, as well as hyperkeratosis of the knees and elbows.

When the chronic stage has been attained in childhood, the skin lesions usually persist without change throughout life, although keratoses of the face, hands, and feet and carcinomatous degeneration may occur at a later age in those individuals who are especially sensitive to the sun. Both of our cases showed typical skin changes, with atrophy, telangiectasias, and hyperpigmentation of sun-exposed areas, especially the face and cheeks and the extensor surfaces of the arms and legs. Case 1 is unusual in that the pigmentary changes, which appeared as freckles over the trunk, limbs, and face, were present at birth. Patient 2 exhibited multiple scattered hemangiomata at birth (which later disappeared) and typical hypo- and hyperpigmentation that began at 4 years of age without a prior erythematous stage.

In this disorder, the scalp hair is usually sparse and fine, but the spectrum ranges from normal hair to total alopecia. There may be a sudden partial or total loss of scalp hair and eyebrows and eyelashes in early childhood. Body hair is absent in the affected skin areas. The nails range from normal to dystrophic or atrophic, and some patients have faulty dentition with microdontia, failure of eruption, and carious tendencies. Both of our patients had fine hair with sparse areas, deficient eyebrows and eyelashes, and carious teeth.

Microcephaly characterized by a triangular, bird-like facies and a high forehead, frontal bossing, and saddle nose that is reminiscent of congenital lues is typically seen. Our patients both have the high forehead and triangular facies. Patient 1 had no supraorbital ridges and a thin, prominent

nose. In Case 2, the frontal bossing, flat nasal bridge, and saddle-nose deformity predominate.

Bilateral cataracts appear suddenly between the ages of 4 and 7 years and occur in 40% to 50% of the reported cases. Patient 1 had no eye anomalies, and patient 2 was unusual in that the bilateral cataracts were congenital. Other eye changes are significantly less common and include degenerative changes of the cornea,[5] microphthalmia with optic atrophy and severe myopia,[3] and colobomata.[6]

• Hypogonadism characterized by small or cryptorchid testes in males and scanty, irregular menses in females and reduced fertility may occur in as many as 25% of cases. Patient 1 experienced normal puberty, and patient 2 is too young for such a determination.

Mental retardation has been reported, but is uncommon. Patient 1 is of normal intelligence; patient 2 had slow developmental landmarks, but the visual and hearing deficits may partially account for her adaptive difficulties.

Short stature with small hands and feet and stubby fingers and toes is estimated to occur in 50% of the patients with Rothmund-Thomson syndrome, although it actually seems to be almost an invariable finding. Less common is severe dwarfism, which has been reported by several authors: Rothmund[1] described a 121-cm tall woman in 1868; Jackli,[7] a 111-cm tall girl, 12 years of age, in 1939; Seefelder,[8] a 121-cm tall man in 1935; Thannhauser,[9] a 149-cm tall, 20-year-old man in 1945; and Castel et al,[10] a 86-cm tall, 10-year-old child in 1977. Our two cases (a 113.8-cm tall, 19-year-old girl, and a 90.0-cm tall, 11-year-old-girl) are additional examples of Rothmund-Thomson-syndrome patients with extreme growth failure. The growth failure in our patients was of prenatal onset, with deficiencies in both birth weight and length. These deficiencies are, in fact, reported but not emphasized in most of the previously reported cases. Sufficient data to construct growth curves or predict adult height are not available from the reported cases.

The absence of the metacarpals and phalanges of the thumbs bilaterally with reduction deformities of the ulnae and radii[3,4] or total absence of the radii[10] have been described. In addition, one patient[10] had bilateral subluxation of the knees like that of case 1. Unilateral split-hand and split-foot deformities have been described in two patients.[11,12] The kyphosis and scoliosis of case 2 is unique, and skeletal asymmetry is rare.[11]

Osteoporosis, as seen in case 1, and patchy sclerosis and cystic changes of the long bones[5,6] are less common changes, as seen on roentgenograms. Short, stubby hands and feet with short toes are uniformly found, yet roentgenogram documentation is insufficient to further characterize the brachydactyly. Probably less than 5% of the patients have other skeletal anomalies such as the unilateral hypoplasia of the radius and/or ulna with or without absence of the thumb as in case 2 or the bilateral radial aplasia with absent thumbs as in case 1. To our knowledge, the sensorineural deafness of patient 2 has not been undescribed as part of this disorder.

The broad spectrum of clinical features of Rothmund-Thomson syndrome is unexplained. Our patients, who had severe but proportionate short stature and skeletal anomalies, meet all the criteria for the diagnosis of this disorder; however, they are unique in that they have primarily skeletal manifestations with typical, although less striking, skin involvement. We suggest that this autosomal recessive disorder should be considered in any patient with severe growth failure, associated skeletal anomalies. and an early onset of typical cutaneous changes.

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William Miller, MD, Thomas Bolton, MD, and David Rimoin, MD provided patient information. Joy Palmer of Shriner's Hospital, Spokane, Wash, did the records search. Lynn Staheli, MD, referred case 2 to us. Leonard Langer, MD, reviewed the roentgenograms. Bonnie McLoughlin and Maxine Covington provided editorial and secretarial assistance.

References

1. Rothmund A: Uber Kataract in Verbindung mit einer eigentumliche Haut degeneration. *Arch Ophthalmol* 14:159-182, 1868.

2. Thomson MS: An hitherto undescribed familial disease. *Br J Dermatol* 35:455-461, 1923.

3. Thomson MS: Poikiloderma congenitale. *Br J Dermatol Syphilol* 48:221-234, 1936.

4. Rook A, Davis R, Stevanovic D: Poikiloderma congenitale, Rothmund-Thomson syndrome. *Acta Derm Venereol* 39:392-420, 1959.

5. Rook A, Whimster I: Congenital cutaneous dystrophy (Thomson's type). *Br J Dermatol Syphilol* 61:197-205, 1949.

6. Taylor WB: Rothmund's syndrome-Thomson's syndrome. *AMA Arch Dermatol* 73:236-243, 1957.

7. Jackli W: Ein Fall von infantiler Poikilodermie (Atrophodermia reticularis cum incontinentia pigmenti) kombiniert mit Alopecie, Mikrodontie und fruhzeitiger Cataracta complicata. *Monatsschr Kinderheilkd* 78:73-81, 1939.

8. Seefelder R: Uber familiares Auftreten von Katarakt und Poikilodermie (Poikilodermia vascularis atrophicans Jakobi). *Z Augenh* 86:81-97, 1935.

9. Thannhauser SJ: Werner's syndrome (progeria of the adult) and Rothmund's syndrome: Two types of closely related heredofamilial atrophic dermatoses with juvenile cataracts and endocrine features: A critical study with five new cases. *Ann Intern Med* 23:559-626, 1945.

10. Castel Y, Masse R, Toudic L, et al: Une Observation de Poikilodermie Congenitale (Syndrome de Rothmund-Thomson) Avec Dystrophies Majeures, Nanisme Tres Severe et Intolerance Digestive. *Ann Pediatr* 24:647-651, 1977.

11. Cole HN, Driver JR, Giffen HK, et al: Ectodermal and mesodermal dysplasia with osseous involvement. *Arch Dermatol Syphilol* 44:773-788, 1941.

12. Hailey H, Hailey H, Cemens H: Poikiloderma congenitale. *Arch Dermatol Syphilol* 44:345-348, 1941.

A Case of Leprechaunism With Severe Hyperinsulinemia

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• This report describes an infant with physical features typical of leprechaunism, including a characteristic facies, hirsutism, and decreased subcutaneous tissue and muscle mass. Intermittent hypoglycemia and severe hyperinsulinemia were documented. The patient's insulin was normal in molecular size and biological activity, but its binding to the patient's cultured fibroblasts was profoundly decreased. Insulin antibodies were not present. A literature review has been undertaken to clarify further the clinical, metabolic, and pathological characteristics of this condition.

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Since the first report of leprechaunism in 1948, we are aware of descriptions in the literature of 24 patients with features typical of this syndrome.[1-22] Infants with leprechaunism fail to thrive and have decreased subcutaneous tissue and muscle mass, a characteristic facies, enlarged genitalia, and hirsutism. Abnormalities of carbohydrate metabolism have been common. This report describes an infant with physical features typical of leprechaunism. Intermittent hypoglycemia and pancreatic islet cell hyperplasia were present. Additional striking features were sustained, severely elevated serum insulin levels and profoundly reduced insulin binding to the patient's cultured skin fibroblasts.

REPORT OF A CASE

The patient, a Canadian Indian male infant, was the third child of parents who were first cousins once removed. His 28-year-old father, 25-year-old-mother, and two older sisters were reportedly healthy. Because the patient's ancestors reside in remote areas, a detailed family history could not be obtained. A maternal first cousin who had unusual facial features was said to have died of starvation at 8 days of age. One of the maternal grandmother's siblings died in infancy and reportedly had unusual physical features. None of the family members was available for detailed clinical or laboratory evaluation. A normal labor and precipitous vaginal delivery followed a full-term, uncomplicated pregnancy during which there was no known teratogenic exposure. There was no history of maternal gestational diabetes. Apgar scores were 4 at one minute and 9 at five minutes. The birth weight was 2.41 kg. Increasing tachypnea and tachycardia necessitated transfer to the Winnipeg (Manitoba, Canada) Children's Centre at 3 days of age.

Physical examination showed a coarsely featured, strikingly hirsute infant who, in spite of his emaciated appearance, was vigorous and cried lustily. Figure 1 illustrates the major physical findings. Measurements were: weight, 2.41 kg (< third percentile); length, 49.5 cm (50th percentile); and head circumference, 35 cm (50th percentile). Abundant dark scalp hair had a reddish tinge in the preauricular regions. The ears were large, low set, and lacked complete cartilaginous development. The eyes were normal. The base of the nose was depressed, and the nares anteverted. The mouth appeared large, the lips thick, and the gingiva hypertrophied. The nipples were prominent and the areolae small; there was no palpable breast tissue. Mild tachypnea was associated with moderate intercostal retraction. The pulse was 180 beats per minute, and the systolic blood pressure was 68 mm Hg. There was a prominent right ventricular heave and a grade 3/6 midsystolic ejection murmur maximal at the midsternal borders. The peripheral pulses were normal. The abdomen was protuberant, the abdominal muscular tone was poor, and a small umbilical

Fig 1.—Patient at 4 days of age, with predominant physical features including loose, wrinkled skin, hirsutism, abdominal distention, prominent external genitalia, depressed nasal bridge, anteverted nares, large mouth, thick lips, and gingival hypertrophy.

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hernia was present. There was no abdominal organomegaly. The penile length was normal (3.5 cm), but the genitalia appeared prominent perhaps because of the lack of surrounding subcutaneous tissue. The skin was dry, deeply pigmented, loosely wrinkled, and covered with excessive, fine, dark hair on the face, back, and extensor surfaces of the limbs. There was a lack of subcutaneous tissue and muscle mass. Joint and neurological examinations showed no abnormalities. The infant had a pronounced musty odor.

LABORATORY FINDINGS

Standard Tests

Values for the following studies were normal: hemoglobin, WBCs and platelets, serum electrolytes, indices of acid-base status, sweat chloride concentration, quinacrine-banded karyotype, immunoglobulins, lymphocyte transformation after concanavalin A and *Candida* mitogenic stimulation, and lymphocytic response and stimulator capacity in allogeneic-mixed lymphocyte cultures.

The BUN level ranged from less than 3 mg/dL initially to 14 mg/dL at 35 days of age. The creatinine clearance was 64 mL/min/sq m at 26 days of age. Proteinuria (346 mg/sq m/24 hr) and intermittent glycosuria were present. Intravenous pyelography demonstrated retention of contrast medium within the collecting tubules of otherwise normal kidneys. The serum bilirubin level was 13.8 mg/dL at 4 days of age and was still elevated (4.9 mg/dL) when last evaluated at 5 weeks of age. Direct reacting components of the total bilirubin ranged from 1.5 to 1.8 mg/dL. The SGOT and alkaline phosphatase values were normal. The total serum protein level was 4.6 g/dL. The chest roentgenogram demonstrated a globular-shaped heart and decreased pulmonary vasculature. There was ECG evidence of biventricular hypertrophy and overload. A right-sided heart catheterization, performed at 4 days of age, demonstrated a moderate left-to-right shunt at the atrial level and a slight narrowing of the main pulmonary arteries. The bone age was compatible with a gestational age of 36 weeks.

The urine contained 3% reducing substances and showed positive reactions to 2,4,-dinitrophenylhydrazine (DNPH) and nitrosonaphthol tests, indicative of α-ketoaciduria and tyrosyluria, respectively.[23] Plasma amino acid thin-layer chromatography demonstrated an elevated tyrosine level of .370 μmole/mL (normal, .069 ± .016[24]). Determination of urinary excretion of tyrosyl substances by gas chromatography and mass spectrometry documented elevations of *p*-hydroxyphenylpyruvic, *p*-hydroxyphenyllactic, and *p*-hydroxyphenylacetic acids. At 36 days of age, after five days of ascorbic acid (vitamin C) therapy (100 mg/day), the reactions to the DNPH and nitrosonaphthol tests were negative and the plasma tyrosine level had decreased to 0.029 μmole/mL.

Table 1.—Simultaneous Glucose and Insulin Levels Before and After Feeding

Age, Days	Values Before (After) Feeding	
	Glucose, mg/dL	Insulin, μU/mL
45	92 (181)	1,580 (2,600)
45	13 (219)	660 (ND)*
46	91	2,480

*ND indicates not determined.

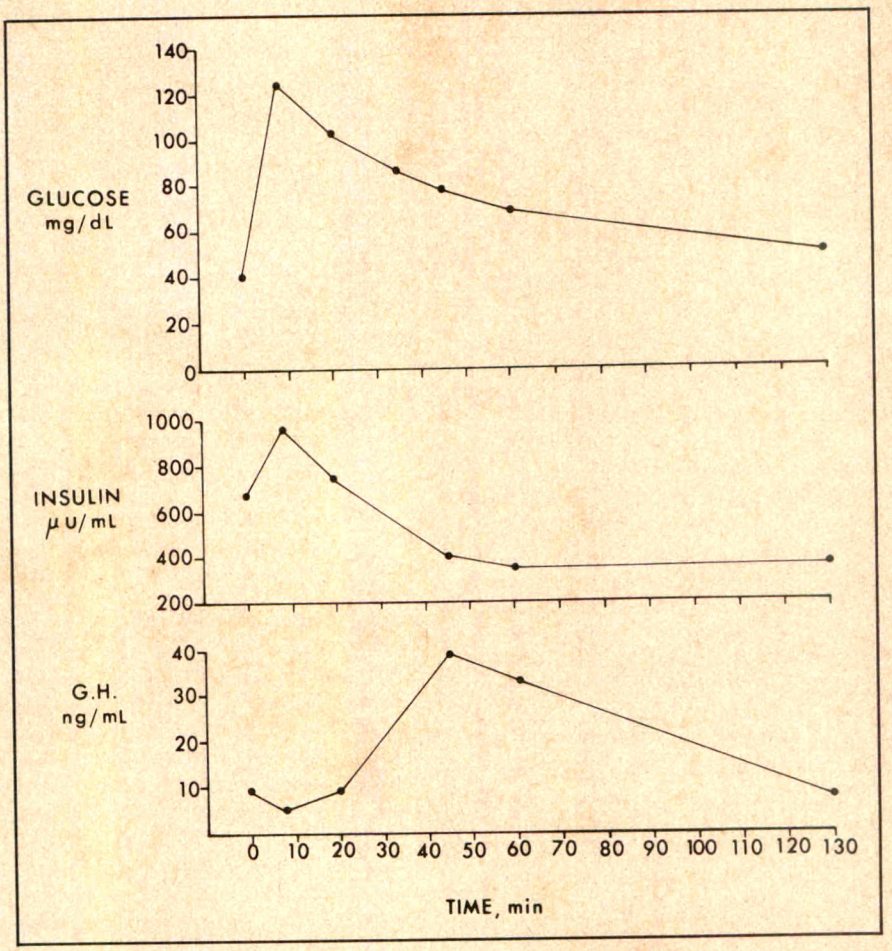

Fig 2.—Plasma glucose, insulin and growth hormone (GH) levels after intravenous injection of 0.5 g/kg of dextrose.

Insulin Resistance

Plasma glucose levels of 43 mg/dL, 133 mg/dL, 90 mg/dL, and 42 mg/dL were obtained during the first 12 days of life. Subsequently, hypoglycemia (plasma glucose ≤ 30 mg/dL) was documented on four occasions with values of 26 mg/dL, 24 mg/dL, 13 mg/dL, and 30 mg/dL at ages 36, 41, 45, and 46 days in spite of oral formula feedings every three hours providing approximately 180 kcal/kg/day. There were no specific clinical signs of hypoglycemia during these episodes. Intravenous

Table 2.—Plasma Values for Patients Mother During Oral Glucose Tolerance Test

Time, hr	Glucose, mg/dL	Insulin, μU/mL
0	89	186
1/2	183	554
1	228	537
2	202	632
3	135	572
4	76	534
5	63	345
6	54	178

and oral dextrose supplementation given during hypoglycemia resulted in rapid stabilization of the plasma glucose level. In all cases, glucose determinations were performed using fresh blood samples obtained from capillary or peripheral venous sites.

Radioimmunoassayed serum insulin levels[25] ranged from 600 to 2,600 μU/mL (normal fasting, 15 μU/mL; normal peak during glucose tolerance testing, 60 to 100 μU/mL). Table 1 lists simultaneous glucose and insulin levels determined immediately before and after feedings. Although insulin levels were consistently elevated when measured at 45 and 46 days of age, the lowest insulin values were obtained when the plasma glucose was correspondingly low, and the highest values were obtained when the plasma glucose level was normal or high.

An intravenous (IV) glucose tolerance test (GTT) was performed at 17 days of age after a six-hour fast. Plasma glucose and immunoreactive insulin[25] and growth hormone[26] levels after IV dextrose administration (0.5 g/kg) are shown in Fig 2. The results indicate normal glucose and growth hormone levels despite sustained hyperinsulinemia. In spite of a borderline low fasting blood glucose level of 40 mg/dL, the corresponding insulin level was high (660 μU/mL). As the blood glucose increased to 125 mg/dL, there was an additional increase in insulin to 960 μU/mL. The rate of glucose disappearance (K_t)[27(p31)] was 1.41%/min. (A normal K_t value from an appropriate control group matched for age, nutritional status, duration of pretest fasting and dose of dextrose is not available. Cornblath et al cited K_t values of 1.65 to 3.50 %/min in infants and children[27(356-367)] and reported a K_t of 0.87 ± 0.11 %/min in low-birth-weight infants less than 3 days of age but significantly higher values in older neonates.[28])

Gel filtration and insulin radioimmunoassay (RIA) of the patient's serum were performed. A 0.5-mL sample of the patient's serum was fractionated on a 50 × 1-cm column (Sephadex G-50) using markers of insulin I 125 and proinsulin I 125.[29] Fractions were assayed by insulin RIA using rabbit antiguinea pig second antibody.[30] The proinsulin peak contained 13% of the immunoreactivity, and the insulin peak 87% of the immunoreactivity, a normal distribution. The void volume showed no apparent immunoreactivity, thereby excluding anti-insulin antibodies. (If anti-insulin antibodies were present, they would bind insulin I 125 but not be precipitated by rabbit antiguinea pig second antibodies since they are human antibodies.) The insulin peak was lyophilized, reconstituted, and assayed in the glucose oxidation bioassay in isolated rat adipocytes.[31] The biological activity (relative to porcine insulin standard) was 70% of the immunoreactivity (on the chromatographed, lyophilized, resuspended sample).

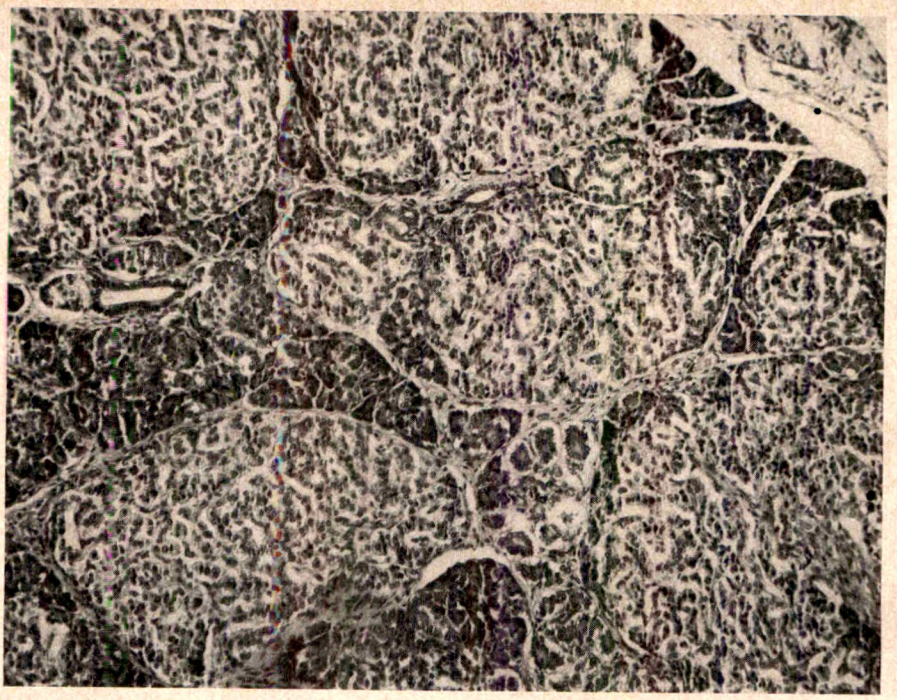

Fig 3.—Pancreas showing striking hyperplasia of islets (hematoxylin-eosin, original magnification ×120).

Table 2 documents the glucose and corresponding insulin levels of this patient's mother, obtained during a six-hour oral GTT that was performed eight months after her son's birth. The values indicate that she also had normal or high plasma glucose levels in the presence of sustained hyperinsulinemia. As her plasma glucose level increased to more than 200 mg/dL, there was an increase of plasma insulin from the fasting level of 186 μU/mL to a maximum of 632 μU/mL at two hours. Since the mother was mildly obese, her obesity may have been a factor contributing to the noted abnormalities of her GTT.

COURSE IN HOSPITAL

The patient fed well but weight gain was poor, and he remained frail and emaciated. Periods of increasing respiratory distress developed in association with intermittent, unexplained abdominal distention. Pneumonia developed at 34 days of age and resolved rapidly with antibiotic therapy; an etiological agent was not isolated. The infant died shortly after the start of diazoxide therapy (10 mg/kg/day), and its effectiveness in controlling glucose homeostasis could not be evaluated.

Death occurred suddenly at 47 days of age and was unassociated with fasting, recent feeding, or any appreciable change in the patient's clinical status in the immediate premortem period.

POSTMORTEM FINDINGS

Notable findings included cardiomegaly (45 g; normal, 26 g) with biventricular hypertrophy, a small (0.2-cm diameter) patent ductus arteriosus, small lymph nodes and thymus, a small firm bile-stained liver, and bilaterally enlarged kidneys with prominent yellow streaks in the renal papillae. There was severe gaseous distention of both small and large bowel and mild dilation of the ureters above the pelvic rim.

Microscopically, the most striking feature was hyperplasia of the pancreatic islets (Fig 3). The islets were increased both in number and in size, and aldehyde fuchsin stains as well as ultrastructural examination confirmed the predominance of β cells. The liver showed dilation of the collecting tubules, most of which contained granular, basophilic casts. Pituitary, thyroid, parathyroids, and testes showed no abnormalities on light microscopy whereas adrenal cortical cells showed moderate lipid depletion. Lymph nodes, though small, had good primary and secondary fol-

licular development, and the thymus showed only stress involution.

COMMENT

We know of detailed reports of 24 cases of leprechaunism originating from four continents and including many racial groups. Table 3 summarizes the predominant historical and physical features of previously reported cases and includes the present patient. Table 4 summarizes the histopathological findings of those patients who have had biopsies or postmortem examinations.

Clinical and Laboratory Features of Leprechaunism

Most of the previously reported patients share many distinguishing physical features, but there are others who are less typical[3,4] and in whom the diagnosis of leprechaunism has been questioned.[6,32] Dallaire et al[32] described three infants with an apparently distinct syndrome of generalized elastic fiber deficiency and leprechaunoid features. Two patients included in the present review also had histopathological confirmation of elastic fiber deficiency[4,18] and may represent additional cases of the syndrome described by Dallaire et al.

A high frequency of parental consanguinity[2,5,12,18,19,22] and familial occurrence[2,12,16,17,22] suggest that leprechaunism is transmitted by an autosomal recessive mode of inheritance. The presence of hyperinsulinemia in our patient's mother further suggests that genetic factors may be important in the etiology of leprechaunism although the mother's mild obesity may have been a factor contributing to her hyperinsulinemia. It is hoped that detailed studies of our patient's family can be undertaken to provide further insight into possible patterns of inheritance. Apart from 46XY Cp+[9] and 46XXGq+[16] karyotypes, chromosomal studies have been normal in the nine cases studied. In their discussion of a 17-month-old female infant, Hopwood and Powell[33] suggested that leprechaunoid features may be manifestations of emotional deprivation; however, this could not be considered an etiological factor in patients with features of leprechaunism present at birth.

The pathophysiology of leprechaunism has not been satisfactorily defined. As was our experience, the comprehensive evaluation of possible pathogenic mechanisms frequently has been limited by the patients' precarious conditions or early deaths.

As in the present case, proteinuria,[1,3,8,14,22] glycosuria,[1,16,21,22] and aminoaciduria[4,5,11,13] have been noted. Elevation of the BUN was reported in four patients,[3,14,18,19] one of whom had an associated increase in serum creatinine.[14] Substantial anatomical renal abnormalities have not been reported. In four cases, including our patient, hyperbilirubinemia was present.[17,20,22] In the two patients in whom the serum thyroxine level was low, the serum triiodothyronine and protein-bound iodine (PBI) levels were normal in one,[15] and the T_3 resin uptake showed increased levels in the other[22]; in four other patients, the PBI value was normal.[4,6,13,14]

By using differential staining techniques, Rogers[8] suggested that the pituitary basophilic predominance noted in three patients represented gonadotrophin-secreting basophils. This suggestion would be consistent with the gonadal enlargement noted in some cases but is inconsistent with the few reports of normal assays of luteinizing and follicle-stimulating hormones.[3,4,6,12,14,22] Autopsy findings frequently have demonstrated small adrenal glands, but in at least two patients, the zona fasciculata was prominent. In the two patients in whom plasma cortisol levels were reported, one had increased levels[14] and the other had normal values.[22] Urinary excretion of 17-hydroxycorticosteroids were normal in a number of other patients.[4,5,11-14,16,17]

Intercurrent infections were fre-

Table 3.—Features of 25 Patients With Leprechaunism

Aspect	No. (%) of Patients
History	
Sex	
Male	8 (32)
Female	17 (68)
Life span	
Early death	16 (64)*
Alive	9 (36)†
Parental Consanguinity	8/23 (35)‡
Physical Features	
Decreased subcutaneous tissue/muscle mass	23 (92)
Large/low-set ears	22 (88)
Enlarged genitalia	19 (76)
Hirsutism	17 (68)
Saddle nose	17 (68)
Loose skin	15 (60)
Prominent breasts/nipples	15 (60)
Developmental delay	11 (44)
Prominent/widely spaced eyes	11 (44)
Birth weight < third percentile	11 (44)
Abdominal distention	11 (44)
Heart murmur	10 (40)
Poor feeding	9 (32)
Large hands and feet	8 (32)
Respiratory distress	8 (32)
Micrognathia	6 (24)
Abdominal hernia	6 (24)
Increased separation of cranial sutures	5 (20)
Hyperpigmentation	4 (16)
Husky cry	4 (16)
Rectal prolapse	3 (12)
Reddish hair	2 (8)
Brachydactylia	2 (8)
Gum hypertrophy	2 (8)

*Mean age of death was 9 months (range, 3 weeks to 8 years). Exclusion of the eldest child reduced the mean age to 2.7 months and the range to 12 months.
†Mean age of those alive at time of their reporting was 12 months (range, 1 week to 3 years).
‡Twenty-three families were represented by 21 individual patients plus two pairs of siblings.

Table 4.—Pathological Findings in Patients With Leprechaunism

Site	Source, Reference No.	Abnormality	% Cases*
Pancreas	1, 2, 5, 7, 8, 15, 17, 20, 22, and present case	Islet cell hyperplasia	67
Gonads	8, 9, 15	Enlarged testes	50†
	1, 2, 7, 17, 22	Enlarged ovaries	56‡
Liver	1, 2, 7-9, 15, 18, 20, 22	Increased iron deposition	60
	1, 2, 7, 15	Increased glycogen deposition	27
Kidney	1, 2, 7-9, 17, 20, 22	Calcific deposits	53
	1, 2, 5, 7, 17, 22	Dilated tubules	43
	Present case	Intratubular basophilic granules	7
Adrenal	1, 2, 7-9, 17, 20	Small	50
	4, 17	Prominent zona fasciculata	13
Lymphoid tissue	1, 2, 5, 8, 11, 22	Decreased	40
Biliary tract	1, 2, 7, 20, and present case	Bile stasis	33
Pituitary	1, 2, 8	Increased basophils	20
	5	Decreased basophils	7
Breast	1, 2	Duct hyperplasia	13
Skin	4, 18	Decreased elastic fibers/ hyperkeratosis	11§
	21	Acanthosis nigricans	6§
Heart	Present case, 22	Ventricular hypertrophy	13
Brain	5, 22	Hypogenesis of cerebellum	13
	11	Absent corpus callosum	7

*All figures represent percentages of 15 autopsied cases unless otherwise indicated.
†Percent of six male subjects.
‡Percent of nine female subjects.
§Percent of 18 patients, three of whom had biopsies performed.

quently noted and included cutaneous abscesses,[1,2,6,7,17] pneumonia,[1,2,5,7,14,18,19] meningitis,[8] and gastroenteritis.[14] Consistent with the findings in our patient, previous reports have reported normal immunoglobulin levels[12,14] and normal T-cell function.[14] Delayed bone age has been a frequent radiological sign, including the present case.[3-6,8,11-13,16,17,20] Nonspecific EEG abnormalities[12,14] and right cortical atrophy on pneumoencephalography[3,14] have been demonstrated.

Carbohydrate Metabolism and Insulin Resistance in Leprechaunism

Of the 20 patients in whom carbohydrate metabolism was evaluated, 18 (90%) were considered by the respective authors to have had biochemical evidence of abnormal glucose homeostasis, including our patient.* Hypoglycemia was reported in seven patients (including the present case)[3,5,6,15,18,19] but was often based on only a single low glucose value. In one case, depletion of glycogen stores as a cause of hypoglycemia is suggested by a negligible increase in blood glucose after adrenalin and glucagon stimulation.[6] Glucose tolerance tests were interpreted as abnormal in seven patients.[5,11,12,14,16,17,21] Excessive elevations of the blood glucose levels were noted during GTTs for three patients,[11,17,21] and in four others, the GTT curves were considered flat.[5,12,14,16] Of the eight patients for whom insulin tolerance tests were performed, two had normal values,[14,16] five demonstrated excessive and prolonged hypoglycemia,[3-6] and one showed a blunted hypoglycemic response.[21]

Elevated blood insulin levels were reported in four patients (including the present case)[18,21,22] and were normal in two others.[9,16] In discussing their patient, Summitt and Favara[11] interpreted as normal a plasma insulin level of 35 mμg/mL (840 μU/mL), but this value seems high. In addition to the present case, one other patient had hyperinsulinemia associated with pancreatic islet cell hyperplasia.[22]

Pancreatic islet cell hyperplasia was noted in eight other cases at autopsy, suggesting that they also may have had hyperinsulinemia. However, a sibling of the patient described in detail by Tsujino and Yoshinaga[17] was reported to have had leprechaunoid features, normal insulin levels, and pancreatic islet cell hyperplasia, indicating that pancreatic hyperplasia may not necessarily reflect hypersecretion of insulin.

Despite the extraordinarily high plasma insulin levels in our patient, hypoglycemia was intermittent, generally mild, and easily corrected by dextrose supplementation. As illustrated in Fig 2, the blood glucose levels were relatively well maintained even in the presence of sustained hyperinsulinemia. The apparent inconsistency between the plasma glucose levels and the severe hyperinsulinemia suggested some degree of insulin resistance. In vivo insulin tolerance testing was not performed for our patient. However, in vitro studies demonstrated that the patient's insulin was normal in size and biological activity. His plasma contained no antibodies to insulin nor to insulin receptors (R. Chochinov, MD, oral communication, June 28, 1978). The binding of insulin I 125 to cultured fibroblasts from this patient and from controls was studied. A profound and selective deficiency of insulin binding to the patients' fibroblasts was observed, indicating a primary defect of insulin receptors.[34] A detailed account of the methodology and results of the insulin binding studies in our patient is described in a separate report.[34]

Jacobs et al[35] and Hill[36] have described an infant with leprechaunoid features, hyperinsulinemia, and a profound decrease in insulin binding to circulating erythrocytes. Whether this insulin receptor defect is genetic (primary) or acquired (secondary) must await the results of fibroblast binding studies.

Kobayashi et al,[21] in their study of a two-year-old girl with leprechaunoid features and marked hyperinsulinemia presented evidence suggesting that their patient's insulin resistance might be due to a cellular defect in the coupling mechanism between insulin receptors and the plasma membrane

*References 3-6, 11, 12, 14-19, 21, 22.

glucose transport system. In their patient, circulating insulin was qualitatively normal, anti-insulin receptor and anti-insulin antibodies were absent, and insulin binding to circulating monocytes was normal.

D'Ercole et al[22] reported insulin resistance in an infant with leprechaunoid features. The insulin of their patient demonstrated chemical and biological characteristics of normal insulin, and insulin I 125 bound normally to cultured fibroblasts. The defect in this patient remains undefined but does not seem to involve a primary abnormality of insulin receptors.

Similarities of physical features between patients reported to have leprechaunism and those with insulin resistance associated with other disorders[37-40] suggest that leprechaunism may not be a distinct clinical entity but may be allied, both clinically and pathophysiologically, with other morphologically similar conditions. For example, patients with leprechaunism have certain similarities to patients with congenital lipodystrophy (lack of subcutaneous fat, insulin resistance) although the patients with lipodystrophy typically exhibit normal or increased growth and well-developed musculature.[37-40]

The group of patients with leprechaunism seems to be heterogeneous with respect to the clinical manifestations exhibited by individual patients and with respect to both the occurrence of insulin resistance and its molecular basis. The exaggerated decrease of blood glucose in response to insulin administration observed in some patients and the normal insulin levels in others suggest that insulin resistance may not be an operative mechanism in all patients with leprechaunoid features. Even among patients with leprechaunism and insulin resistance, however, our patient seems to be unique in having a genetic abnormality of his insulin receptors as a presumed basis for insulin resistance.

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Nonproprietary Name and Trademarks of Drug

Diazoxide—*Proglycem, Hyperstat.*

References

1. Donohue WL: Clinicopathologic conference at the Hospital for Sick Children: Dysendocrinism. *J Pediatr* 32:739-748, 1948.

2. Donohue WL, Uchida I: Leprechaunism. *J Pediatr* 45:505-519, 1954.

3. Evans PR: Leprechaunism. *Arch Dis Child* 30:479-483, 1955.

4. Patterson JH, Watkins WL: Leprechaunism in a male infant. *J Pediatr* 60:730-739, 1962.

5. Salmon MA, Webb JN: Dystrophic changes associated with leprechaunism in a male infant. *Arch Dis Child* 38:530-535, 1963.

6. Dekaban A: Metabolic and chromosomal studies in leprechaunism. *Arch Dis Child* 40:632-636, 1965.

7. Kálló A, Lakatos I, Szijártó L: Leprechaunism (Donohue's syndrome). *J Pediatr* 66:372-379, 1965.

8. Rogers DR: Leprechaunism (Donohue's syndrome). *Am J Clin Pathol* 45:614-619, 1966.

9. Ferguson-Smith MA, Hamilton W, Ferguson IC, et al: An abnormal metacentric chromosome in an infant with leprechaunism. *Ann Genet* 11:195-200, 1968.

10. Patterson JH: Presentation of a patient with leprechaunism, in Bergsma D (ed): *Clinical Delineation of Birth Defects IV: Skeletal Dysplasias.* Baltimore, Williams & Wilkins Co, 1969, pp 117-121.

11. Summitt RL, Favara BE: Leprechaunism (Donohue's syndrome): A case report. *J Pediatr* 74:601-610, 1969.

12. Der Kaloustian VM, Kronfol NM, Takla R, et al: Leprechaunism: A report of two new cases. *Am J Dis Child* 122:442-445, 1971.

13. Poradovska W, Jaworska M, Hanc I: Donohue's syndrome (leprechaunism) in a female infant. *Acta Chir Plast* 14:4-12, 1972.

14. Gross-Kieselstein E, Ben-Galim E, Amir N, et al: Leprechaunism (Donohue syndrome). *Am J Dis Child* 126:500-503, 1973.

15. Ordway NK, Stout LC: Intrauterine growth retardation, jaundice and hypoglycemia in a neonate. *J Pediatr* 83:867-874, 1973.

16. Iwasaki H, Abe M, Nawate G, et al: A case of chromosome abnormality (46, XX, Gq+) with congenital heart disease and leprechaunism. *Jpn J Hum Genet* 19:82-83, 1974.

17. Tsujino G, Yoshinaga T: A case of leprechaunism and an analysis of some clinical manifestations of this syndrome. *Z Kinderheilkd* 118:347-360, 1975.

18. Hartdegen RG, Dogliotti M, Rabinowitz L, et al: Leprechaunism. *Br J Dermatol* 93:587-591, 1975.

19. Ramaat LG, Shafi KM, Dajani FF: Donohue's syndrome (report of a case). *Indian Pediatr* 14:325-327, 1977.

20. Adams JM, Gordon LP, Dutton RV, et al: Leprechaunism (Donohue's syndrome) in a low birth weight infant. *South Med J* 70:998-1001, 1977.

21. Kobayashi M, Olefsky JM, Elders J, et al: Insulin resistance due to a defect distal to the insulin receptor: Demonstration in a patient with leprechaunism. *Proc Natl Acad Sci USA* 75:3469-3473, 1978.

22. D'Ercole AJ, Underwood LE, Groelke J, et al: Leprechaunism: Studies of the relationship among hyperinsulism, insulin resistance and growth retardation. *J Clin Endocrinol Metab* 48:495-502, 1979.

23. Perry TL, Hansen S, MacDougall L: Urinary screening tests in the prevention of mental deficiency. *Can Med Assoc J* 95:89-95, 1966.

24. Scriver CR, Rosenberg LE: *Amino Acid Metabolism and Its Disorders.* Toronto, WB Saunders Co Canada Ltd, 1973, p 42.

25. Morgan CR, Lazarow A: Immunoassay of insulin: Two antibody systems: Plasma insulin levels of normal, subdiabetic and diabetic rats. *Diabetes* 12:115-126, 1963.

26. Schalch DS, Parker ML: A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature* 203:1141-1142, 1964.

27. Cornblath M, Schwartz R: *Disorders of Carbohydrate Metabolism in Infancy,* ed 2. Toronto, WB Saunders Co Canada Ltd, 1976.

28. Cornblath M, Wybregt SH, Baens GS: Studies of carbohydrate metabolism in the newborn infant: VII. Tests of carbohydrate tolerance in premature infants. *Pediatrics* 32:1007-1024, 1963.

29. Gorden P, Hendricks CM: The measurement of plasma insulin and proinsulin-like components, in Croll MN, Wallner R, Honda T (eds): *New Techniques in Tumor Localization and Radioimmunoassay.* New York, John Wiley & Sons Inc, 1974, pp 17-24.

30. Yalow RS, Berson SA: Immunoassay of endogenous plasma insulin in man. *J Clin Invest* 39:1157-1175, 1960.

31. Kahn CR, Baird K, Flier JS, et al: Effects of autoantibodies to the insulin receptor on isolated adipocytes. *J Clin Invest* 60:1094-1106, 1977.

32. Dallaire L, Cantin M, Melançon SB, et al: A syndrome of generalized elastic fiber deficiency with leprechaunoid features: A distinct genetic disease with an autosomal recessive mode of inheritance. *Clin Genet* 10:1-11, 1976.

33. Hopwood NJ, Powell GF: Emotional deprivation: Report of a case with features of leprechaunism. *Am J Dis Child* 127:892-894, 1974.

34. Schilling EE, Rechler MM, Grunfeld C, et al: Primary defect of insulin receptors in skin fibroblasts cultured from an infant with leprechaunism and insulin resistance. *Proc Natl Acad Sci USA* 76:5877-5881, 1979.

35. Jacobs RF, Nestrud RM, Beard AG, et al: An inherited syndrome of hyperglycemia, hyperinsulinemia and failure to thrive: Possible insulin receptor defect, abstracted. *Clin Res* 26:71A, 1977.

36. Hill DE: Effect of insulin on fetal growth. *Semin Perinatol* 2:319-328, 1978.

37. Seip M: Lipodystrophy and gigantism with associated endocrine manifestations: A new diencephalic syndrome? *Acta Paediatr Scand* 48:555-574, 1959.

38. Oseid S: Studies in congenital generalized lipodystrophy (Seip-Bernardinelli syndrome). *Acta Endocrinol* 72:475-494, 1973.

39. Najjar SS, Salem GM, Idriss ZH: Congenital generalized lipodystrophy. *Acta Paediatr Scand* 64:273-279, 1975.

40. Huseman C, Johanson A, Varma M, et al: Congenital lipodystrophy: An endocrine study in three siblings. *J Pediatr* 93:221-226, 1978.

Fever Phobia

Misconceptions of Parents About Fevers

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• Eighty-one parents bringing their children to a hospital-based pediatric clinic were surveyed about their understanding of fever. Most parents were unduly worried about low-grade fever, with temperatures of 38.9 °C or less. Their overconcern was designated "fever phobia." Most parents (52%) believed that moderate fever with a temperature of 40 °C or less can cause serious neurological side-effects. Hence, most parents treated fever aggressively: 85% gave antipyretic medication before the temperature reached 38.9 °C and 68% sponged the child before the temperature reached 39.5 °C. A review of the literature showed that the only serious complications of fever were febrile status epilepticus and heat stroke, two rare entities. The great concern of parents about fever is not justified. Health education to counteract "fever phobia" should be a part of routine pediatric care.

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A controversy in medical theory and practice since ancient times has been the question of whether a physician ought to fight fever, ignore it, or encourage it. For ancient humoral pathologists, fever was the most important of the body's natural defenses when the amount of "phlegm" in the body increased. The doctrine stated that the heat of fever was designed to drive the excess phlegm out of the body. Fevers were encouraged and celebrated. By the middle of the 19th century, Claude Bernard had completed his experiments on the overheating of animals and had proven that death quickly occurred if the body's temperature rose 5 to 6 °C above normal.[1] Thereafter, fever gradually was looked on as injurious to health, and treatment with antipyretic medication was considered essential.

Although modern physicians have achieved a more balanced perspective on the treatment of fever, many parents seem to be as fearful of fever as physicians were a century ago. The purpose of this study was to determine the prevalence of parental misconceptions about the dangers of fever and the home treatment of fever. The literature was reviewed in an attempt to delineate the level of fever that is harmful and what the harmful effects are.

SUBJECTS AND METHODS

One hundred parents bringing their children to a university-based walk-in clinic were asked to complete a one-page questionnaire on their understanding of fever while waiting to see a physician. Many of the children were not acutely ill at the time of the visit. Eighty-one parents completed the questionnaire and returned it to a member of the clinic staff. The parents were given no assistance with answering the questions, but on completion of the questionnaire, the clinic nurse reviewed the appropriate answers with the parents as time permitted. Fifty-seven percent of all the families surveyed had one child, 32% had two, 12% had three, and 9% had four or more.

Of note is the fact that 14% of all the families had an only child younger than 6 months of age and hence their past experience with febrile illnesses may have been limited. Generally speaking, 50% of all the families seen in this clinic are medically indigent, 40% are part pay, and 10% pay the full fee. The questions asked in the questionnaire were as follows. (1) What do you consider a "high" fever? (2) If your child had a fever and you didn't treat it with aspirin or acetaminophen (Tylenol), how high could it go? (3) In your opinion, what is the greatest harm that *high* fever can cause to a child? (4) How *low* a temperature can cause the types of harm you listed in question 3? (5) How worried are you about what fevers can do? (6) If your child has fever, how often do you continue to take his temperature? (7) Above what temperature do you give aspirin or acetaminophen? (8) How often do you give aspirin or acetaminophen for fever? (9) If your child has fever when you put him down for the night, do you awaken him or her during the night to

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give acetaminophen or aspirin? (10) Above what temperature would you sponge your child? (11) How did you learn your ideas about fever: from what your doctor or nurse does when you bring your child in with fever; from what physicians and nurses have told you; from friends and relatives; from reading.

RESULTS

Figures given in Table 1 shows that 58% of all parents consider fevers of 38.9 °C (102 °F) or less to be "high fevers." Those given in Table 2 show that 16% of all parents think an untreated fever can keep rising to 43.3 °C (110 °F) or higher. Anyone holding this misconception would probably fight fever as if their child's life depended on it.

Results given in Table 3 remind us that 94% of all parents believe fever can cause side-effects, and 62% believe it can cause permanent harm, the most common concern being "brain damage." Table 4 contains the parents' definitions of a "dangerous fever," the level of fever that can cause the harmful effects listed in Table 3. Surprisingly, 52% of all parents believe that these serious and rare complications can occur with fevers of 40 °C (104 °F) or less, and 18% believe these can be caused by fevers of 38.9 °C (102 °F) or less.

The responses to question 5 show that 63% of all parents "worry lots" about possible harmful effects from fever, 36% "worry some," and only 1% did not worry. The responses to question 6 demonstrate that 8% of all parents take, or think they should take, their child's temperature every hour if the child is febrile. This behavior probably points to a concern that the temperature may rise quickly. Thirty-five percent of all parents took the temperature five to eight times per day.

Table 5 demonstrates that 56% of all parents give antipyretic medications for temperature of 37.0 to 37.8 °C (ie, possibly normal temperatures). A total of 85% give antipyretic medications before the temperature reaches 38.9 °C (102 °F). The responses to question 8 confirm that most parents know the correct interval for giving antipyretic medication, but that 7% may give it inadequately (one to two times per day) and 4% may inadvertently overdose their child (by giving it every one to two hours).

Table 1.—Parent's Definition of a 'High Fever'

°C	°F	% of Parents
37.8	100	12
38.4	101	11
38.9	102	35
39.5	103	32
40.0	104	8
40.6	105	2

Table 2.—Parent's Understanding of How High a Fever Can Go If They Do Not Treat It

°C	°F	% of Parents
40.6	105	52
41.7	107	32
43.3	110	9
45.0	113	2
46.1	115	1
48.9	120	4

Table 3.—Parent's Understanding of Harmful Effects of High Fever

Type of Harm	% of Parents
Brain damage	46
Convulsions	15
Death	8
Coma	4
Dehydration	4
Blindness	3
Deformities	1
Delirium	1
Very sick	12
No response	6

Table 4.—Parent's Definition of Lowest Temperatures That Can Cause Type of Harm Listed in Table 3

°C	°F	% of Parents
37.8	100	4
38.4	101	7
38.9	102	7
39.5	103	8
40.0	104	26
40.6	105	27
41.1	106	6
41.7	107	6
42.2	108	3
43.3	110	6

Table 5.—Temperatures Above Which Parents Would Give Antipyretic Medications

°C	°F	% of Parents
37.0	98.6	11
37.8	100	45
38.4	101	29
38.9	102	8
39.5	103 or higher	7

Table 6.—Temperatures Above Which Parents Would Initiate Sponging

°C	°F	% of Parents
37.8	100	7
38.4	101	14
38.9	102	42
39.5	103	30
40.0	104	6
41.1	106	1

The responses to question 9 showed that 48% of all parents are so worried about fever that they would awaken their child to give additional medication. Table 6 shows that 20% of all parents would sponge their child if the temperature reached 37.8 to 38.4 °C (100 to 101 °F), and an additional 42% would sponge if it reached 38.9 °C (102 °F).

Table 7 reminds us that health personnel are important teachers of parents concerning fevers. Some 51% of all parents credit physicians and nurses with being their main source of information. This group of parents and the two groups that stated they learn about fevers from other sources were compared in terms of how often they gave inappropriate responses to the previous nine questions. No significant differences were found on the χ^2 tests. There was a suggestion, however, that the group who relied on reading more frequently gave appropriate answers.

Table 7.—Parent's Source of Information About Fevers

Source of Information	% of Parents
What doctors or nurses said	34
What doctors or nurses did	17
Friends or relatives	30
Reading	19

Overall, the answers to questions 1, 2, and 5 suggest that many parents are unduly worried about fevers. Tables 3 and 4 suggest that most parents worry about serious permanent damage from fevers. It is therefore not surprising that most parents treat fevers overaggressively, as seen by the responses to questions 7, 9, and 10.

COMMENT

The evidence clearly shows that many parents are greatly concerned about fevers in their children. In fact, some worry about a universal phenomenon, the low-grade acute fever that every child experiences repeatedly. Because this fear is unrealistic, this condition has been designated "fever phobia." The literature was reviewed on three related topics: the maximal levels of fever reported in children with acute infectious diseases, the level of fever that can cause harm, and what those harmful effects are. There are also some suggestions for counteracting fever phobia.

The Highest Level of Fever in Children With Infectious Diseases

Hyperpyrexia is generally defined as a temperature of 41.0 °C or greater. Fevers of this magnitude are rare. Tomlinson's study[2] on high fevers in ambulatory patients during 13 years of private pediatric practice reported temperatures of 40.0 to 40.5 °C in 78 children, 40.5 to 41.0 °C in 28 children, and higher than 41.1 °C in two children. In a large pediatric emergency room, McCarthy and Dolan[3] found 100 children with temperatures of 41 °C or greater over an eight-year span. The incidence was one child with hyperpyrexia for 2,100 patient visits.

Studies of inpatients have found a higher incidence of hyperpyrexia. Akerren[1] reviewed inpatient records for the highest recorded temperature and found that 1.5% of all children have a temperature reading of 41.0 °C or greater. DuBois[4] examined the charts of 357 adult patients with diseases noted for high fever, namely pneumonia, relapsing fever, malaria, and induced malaria. These patients had 1,761 temperature readings recorded, and of these readings 4.3% were above 41.1 °C and none were above 42 °C. DuBois concluded that "an emergency regulatory mechanism exists that sharply limits the temperature at the level of about 41.1 °C (106 °F)."

If common infectious diseases are an unusual cause of hyperpyrexia, what are the usual causes of temperatures greater than 41.1 °C (106 °F)? Between 41.1 and 41.7 °C (106 and 107 °F), infections of the CNS play an important role, presumably due to the direct effect of the infection on the hypothalamus. In McCarthy and Dolan's study,[3] 10% of all the children with hyperpyrexia had bacterial meningitis and 3% had aseptic meningitis. In Akerren's study,[1] 15% of all the children with hyperpyrexia had acute CNS disease (mainly meningitis) and 33% had underlying chronic brain defects, such as trisomy 21, hydrocephalus, brain tumor, and mental retardation. In DuBois' study,[4] the highest temperatures were recorded in patients with malaria, and one can speculate that some of the patients had cerebral malaria. Most temperatures above 41.7 °C in children without CNS disease are due to human error from excessive heat load or from interference with heat loss. Examples are wrapping a febrile child in too much clothing or blankets, covering a child with burns or eczema in too many dressings, placing a baby near a radiator, placing a child in a car in direct sunlight, or placing a child in a homemade steam tent.[5] All of these errors are more dangerous during a heat wave. One study on hyperpyrexia found that 64% of all the cases occurred between June and September, supporting the view that ambient temperature may be a factor.[6] Rarely, a child develops hyperpyrexia because of physical exertion while receiving a medication that prevents sweating (eg, phenothiazine or atropine).[7]

The Harmful Level of Fever

Discomfort with fever usually does not begin until the temperature reaches 39.5 or 40.0 °C (103 or 104 °F). Every physician has seen children who are happy and playful and who to everyone's surprise are found to have a temperature of this level. DuBois[4] reported temperatures to 40.0 °C that occurred after hard exercise. Newburgh[8] reported temperatures of 41.0 °C (105.8 °F) in persons at the end of a three-mile race. Obviously, acute fevers of this level cannot be considered dangerous. In their treatment of neurosyphilis, fever therapists produced and maintained fevers of 42 °C (107.6 °F) in patients for eight to ten consecutive hours by using a hyperthermia cabinet set at 54.4 °C (130 °F).[9] Although many of the patients experienced disorientation and vomiting, heat stroke was uncommon and the mortality was less than 0.5% when appropriate means were used to correct dehydration and hypoxia.[9] Artifically induced fevers of 41.5 to 42.0 °C for several hours are currently being used in some centers to treat metastatic tumors.[10,11] Sharp regression of the tumor is seen in some patients.

The literature was reviewed for statements on dangerous or harmful levels of fever. The information obtained is given in Table 8. Most of the warnings relate to a breakdown of the heat regulatory mechanisms (ie, heat stroke). Few data could be found on the relationship of body temperature to cellular death of normal cells. Recent studies have shown that tumor cells are more thermal sensitive than are normal cells.[10] Only three authors mention studies or case reports.[1,4,8] Relevant comments were found in one pathology textbook,[12] three physiology textbooks,[13-15] and three pediatrics textbooks.[16-18] Although the data leave much to be desired, the consensus seems to be that temperatures under 41 °C are relatively harmless, that most people can tolerate temperatures of between 41 and 42 °C without a heat stroke developing and temperatures over 42 °C are usually harmful.

The Harmful Effects of Fever

Fever rarely causes any permanent harm. Dehydration can occur due to increased fluid loss with sweating, but this is preventable with attention to the child's thirst and fluid needs. Delirium or toxic encephalopathy can be caused by febrile illnesses as well as other nonfebrile disorders.[19] Delirium is more an inconvenience than a threat to the child's well-being. Since more than 50% of all children with meningitis have associated delirium, this diagnosis should always be considered in delirious children.[20] The two complications of fever that can lead to permanent bodily harm are febrile status epilepticus and heat stroke.

Heat stroke can be defined as a catastrophic condition characterized

Table 8.—Definitions of Harmful or Dangerous Temperatures From the Literature

Source	Definition of Harmful Temperature, °C (°F)	Comments by Author
Dubois[4]	41	Harmful
	42	Dangerous if prolonged
Akerren[1]	42	Fatal outcome rapidly occurs
Newburgh[8]	43	Upper limit of human temperature, few survivors above this
Florey[12]	41.1 (106)	Heat regulating mechanism starts to fail
	43.3	Coma
Ganong[13]	41.1 (106)	Some brain damage if prolonged
	43	Death is common
Guyton[14]	41.7 (107)	Heat regulating mechanism starts to fail
	43.3 (110)	Death in a few hours
Vander et al[15]	41.1 (106)	Harmful
	41.7 (107)	Convulsions
	43.3 (110)	Death
Frothingham[16]	41	Heat stroke may occur
Pascoe and Grossman[17]	41.1 (106)	High fever, but not an emergency
Ryan[18]	41.1 (106)	Possibly dangerous*

*This author, however, has described nine patients with temperatures above 108 °F who did not have sequelae.

by hyperpyrexia (usually over 42.0 °C), delirium, coma, and anhidrosis.[21] Heat stroke appears to result from a breakdown in the hypothalamic heat regulatory mechanism. Without treatment, the mortality can be as high as 80% and the survivors can have neurological deficits, including cerebellar ataxia and severe dysarthria.[21] Of note, during a Cincinnati heat wave, every patient with heat stroke whose temperature on admission to the hospital was less than 41.7 °C survived.[22] The incidence of neurological sequelae was not recorded. Heat stroke should rarely occur with the usual childhood febrile illnesses unless the child is excessively clothed, the site of infection is the CNS, or the child has an underlying disease that limits sweat production (eg, anhydrotic ectodermal dysplasia).

A febrile seizure is the best-known complication of a high fever, and such seizures occur in 4% of all children with high fever.[23] Whether or not simple febrile seizures per se lead to permanent neurological sequelae is controversial. The incidence of afebrile seizures in children who have experienced febrile seizures is 2%, which is greater than the incidence of seizures in the general population.[24] It is doubtful that children with febrile seizures have an increased incidence of mental retardation or learning disorders.[25]

Febrile status epilepticus can be defined as a febrile seizure lasting longer than 60 minutes.[26] Seizures of this duration occur in 1%[27] or 2%[23] of all children with febrile seizures. These prolonged febrile seizures can cause severe brain damage. The damage is probably due to hypoxia associated with the seizure or to aspiration and airway obstruction.[23,28] Millichap[23] found evidence of subsequent brain damage in less than 0.2% of all children with febrile seizures. These figures suggest that status epilepticus can occur without subsequent brain damage.

The physician should attempt to prevent febrile status epilepticus. The only treatment regimen proven to be effective in preventing the recurrence of febrile seizures is administration of continuous prophylactic phenobarbital.[27,29] Once a seizure begins, it should be treated vigorously to prevent any progression into status epilepticus. Bringing the temperature below the seizure threshold for that child is probably the most practical approach.[23]

One question that remains unanswered is whether or not the first febrile seizure could be prevented by vigorous early treatment of all suspected infections with antipyretics. No study has yet proved that vigorous treatment with antipyretics is effective in decreasing the number of febrile seizures. Two pieces of information make this notion doubtful. At the time of onset of febrile seizures, 30% of all parents are unaware of the presence of a fever, in 61% of all cases the fever has been present less than 12 hours, and in 81% of all cases the fever has been present less than 24 hours.[27] In addition, febrile convulsions can occur in the face of moderate temperature elevations. Wolf et al[27] found that 81% of all seizures occurred at 40.0 °C or less, and Millichap[30] found that 50% of all cases of febrile convulsion occurred at 40.0 °C or less, with a range of 38.5 to 41.4 °C. Therefore, it seems likely that a febrile seizure can occur despite the utmost vigilance and the use of antipyretics.

Guidelines for Counteracting Fever Phobia

Fever phobia is an unnecessary burden for parents. Physicians and nurses who provide medical care for children can help parents gain a better perspective on fever. Fever can be discussed at the fourth- or sixth-month health supervision visit in anticipation of the inevitable febrile illnesses to come. We can emphasize that fevers do not automatically require therapy.[31] We can stress with parents that the harmful effects of fever are rare. We can underscore the fact that fever is the body's normal response to infection and may even have some beneficial effects. Indeed, fever has been shown to limit the replication of some common viruses.[32] The following ten guidelines may prove helpful for counseling parents.

(1) Define fever as a temperature over 37.8 °C (100 °F) orally or 38.0 °C (100.5 °F) rectally. On a warm day, a child who has a temperature of between 38.0 and 38.5 °C should have his temperature taken again after he has had a half hour to cool off, before making a diagnosis of fever. We can define a high fever as a temperature

higher than 40.5 °C (105 °F) and mention that harm from fever does not begin until the temperature is 41.1 or 41.7 °C (106 or 107 °F).

(2) Use the term "fever therapy" rather than "fever control." Fever control may imply that the fever will go out of control if the parent does not do something about it quickly. Physicians can remind parents that the body has a thermostat for the purpose of controlling fever and this thermostat generally keeps the body temperature below 41.1 °C (106 °F). We can remind parents that the temperature will not climb upward relentlessly.

(3) Recommend treating the child's condition with antipyretic medications only if the temperature is over 39 °C (102 °F) and, preferably, only if the child is uncomfortable. If the child is hospitalized, any standing order that is written for fever medication should also specify the level of fever to be treated. Mention to the parents that low-grade fevers do not require any antipyretic treatment except light clothing and additional fluids. Also, mention that the main reason for treating fever is to help the child feel comfortable, not to prevent harm to the child. In my experience, many physicians who intellectually agree with these indications for medication still tend to prescribe antipyretics for any patient with fever they are consulted about by telephone.

(4) Recommend sponging the child with water (37 °C) only if the temperature is higher than 40 °C (104 °F), has not responded to treatment with antipyretics, and the patient is uncomfortable. The antipyretic must be given one hour before sponging so the hypothalmic set point will be lowered. If sponging is administered before the antipyretic is given, the child experiences discomfort and shivering because the hypothalamus attempts to offset the lowering of the body temperature, and the temperaure quickly returns to the previous level after the sponging is discontinued.[33]

Thirteen current pediatrics textbooks were searched for guidelines about the use of antipyretic medications and/or sponging. Six textbooks had no section on fevers.[34-39] Two textbooks had sections on fever, but no specific recommendations.[40,41] The five textbooks with specific guidelines recommended giving antipyretics for temperatures over 39.0 or 39.5 °C and sponging for temperatures over 39.5 to 40 °C.[16-18,42,43]

(5) Assume a calm approach to fevers. Physicians and nurses serve as models for parents' later behavior around illness. In our offices and clinics, we should not respond to fever as if it were a crisis. We should avoid rapid sponging or keeping the child in the clinic until we bring the temperature below some magic number such as 38 °C. Obvious exceptions to these statements include the child with a temperature over 41.0 °C or who has a febrile seizure. Physicians who obtain routine temperatures on all children who come to the office may also be overemphasizing the importance of undetected fevers in the minds of the parents.

(6) Suggest that the parents not give alternating dosages of acetaminophen and aspirin every two hours. This aggressive approach may suggest to the parents that fever is a grave situation. There is no reported study of the two-hour alternate aspirin-acetaminophen treatment regimen. Only one pediatrics textbook mentions it.[16] One study, comparing a combination of aspirin and acetaminophen to each drug used alone, showed a prolonged six-hour effect from the combination.[44] The combination might be appropriate for a child who has fever at bedtime. One risk of using alternate drugs at two-hour intervals is that if the parents run out of the acetaminophen, they may switch to giving aspirin every two hours and thus cause salicylism.

(7) Suggest that parents not awaken the child from sleep for temperature-taking or administration of antipyretics. Remind them that sleep is valuable for a sick child.

(8) The temperature should be taken before every dose of antipyretic medication to make certain the child does not receive unnecessary medications. On a practical level, very few parents are willing to carry out this instruction. A more reasonable recommendation is to ask parents to repeat giving the medication without taking the temperature if the child is uncomfortable, but to retake the temperature if they are uncertain whether the child still has a fever. The parents should also retake the temperature if the patient is uncomfortable despite treatment and seems extremely hot. This measure would help to recognize any child who has a temperature over 41.0 °C.

(9) Provide special recommendations for the child who has experienced a febrile seizure. The parents of these children want to be involved in a vigorous antipyretic program, whether it is helpful or not. These children can be treated with antipyretic medications at the first sign of fever. This medication should probably be given every four hours for a minimum of 24 hours, since 81% of all febrile seizures will occur in this time span.[27] Awakening the child once during the night to give an antipyretic drug might be a reasonable thing to do, and sponging is an important part of the home first aid for any febrile seizure.

(10) Teach parents that observation of their child's symptoms and signs is more important than the temperature. Emphasize that temperature-taking can never substitute for these more important observations. Parents can be reminded that the main reason for consulting a physician about fever is the presence of worrisome symptoms, such as difficulty with breathing, dysuria, delirium, whimpering, irritability, or pain. The physician usually does not need to be consulted for fever alone, unless it is high (40.6 °C [105 °F] or above), the child is younger than 3 months of age with any fever, the fever persists longer than 24 hours without an obvious site of infection, if the fever persists over 72 hours in any illness, or if the child has a serious underlying disease.

Brian A. Lauer, MD, gave a critical appraisal of this manuscript.

References

1. Akerren Y: On hyperpyretic conditions during infancy and childhood. *Acta Pediatr* 31:1-72, 1943.

2. Tomlinson WA: High fever. *Am J Dis Child* 129:693-696, 1975.

3. McCarthy PL, Dolan TF: Hyperpyrexia in children. *Am J Dis Child* 130:849-851, 1976.

4. DuBois EF: Why are fever temperatures

over 106 °F rare? *Am J Med Sci* 217:361-368, 1948.

5. Roberts KB, Roberts EC: The automobile and heat stress. *Pediatrics* 58:101-104, 1976.

6. Simon HB: Extreme pyrexia. *JAMA* 236:2419-2421, 1976.

7. Greenblatt DJ, Greenblatt GR: Chlorpromazine and hyperpyrexia: A reminder that this drug affects the mechanisms which regulate body temperature. *Clin Pediatr* 12:504-505, 1973.

8. Newburgh LH: *Physiology of Heat Regulation.* Philadelphia, WB Saunders Co, 1949.

9. Wallace J, Bushby SRM: Hazards of hypertherm treatment. *Lancet* 2:459-464, 1944.

10. Hyperthermia in the treatment of the cancer patient. *Cancer* 37(April suppl):2075-2083, 1976.

11. Miller RC, Connor WG, Heusinkveld RS, et al: Prospects for hyperthermia in human cancer therapy. *Radiology* 123:489-495, 1977.

12. Florey L: *General Pathology*, ed 4. Philadelphia, WB Saunders Co, 1970.

13. Ganong WF: *Review of Medical Physiology*, ed 8. Los Altos, Calif, Lange Medical Publications, 1977.

14. Guyton AC: *Basic Human Physiology: Normal Function and Mechanisms of Disease*, ed 2. Philadelphia, WB Saunders Co, 1977.

15. Vander AJ, Sherman JH, Luciano DS: *Human Physiology: The Mechanisms of Body Function*, ed 2. New York, McGraw-Hill Book Co Inc, 1975.

16. Frothingham TE: Fever, in Green M, Haggerty RJ (eds): *Ambulatory Pediatrics II.* Philadelphia, WB Saunders Co, 1977.

17. Pascoe DJ, Grossman M (eds): *Quick Reference to Pediatric Emergencies.* Philadelphia, JB Lippincott Co, 1973.

18. Ryan JF: High fever, in Gellis SS, Kagan BM (eds): *Current Pediatric Therapy*, ed 8. Philadelphia, WB Saunders Co, 1978.

19. Weiner MF: Hallucinations in children. *Arch Gen Psychiatry* 5:54-63, 1961.

20. Wallace JF: Infectious delirium. *Southwestern Med* 50:181-183, 1969.

21. Knochel JP: Environmental heat illness. *Arch Intern Med* 133:841-864, 1974.

22. Ferris EB Jr, Blankenhorn MA, Robinson HW, et al: Heat stroke: Clinical and chemical observation on 44 cases. *J Clin Invest* 17:249-257, 1938.

23. Millichap JF: *Febrile Seizures.* New York, The Macmillan Co Publishers, 1968.

24. Nelson KB, Ellenberg JH: Predictors of epilepsy in children who have experienced febrile seizures. *N Engl J Med* 295:1029-1033, 1976.

25. Ouellette EM: Managing febrile seizures. *Drug Therapy* 2:37-39, 1977.

26. Aicardi J, Chevrie JJ: Convulsive status epilepticus in infants and children. *Epilepsia* 11:187-197, 1970.

27. Wolf SM, Carr A, Davis DC, et al: The value of phenobarbital in the child who has had a single febrile seizure: A controlled prospective study. *Pediatrics* 59:378-385, 1977.

28. Fowler M: Brain damage after febrile convulsions. *Arch Dis Child* 32:67-76, 1957.

29. Pollack MA: Continuous phenobarbital treatment after a "simple febrile convulsion." *Am J Dis Child* 132:87-89, 1978.

30. Millichap JG: Studies in febrile seizures: I. Height of body temperature as a measure of the febrile seizure threshold. *Pediatrics* 23:76-85, 1959.

31. Done AK: Uses and abuses of antipyretic therapy. *Pediatrics* 23:774-780, 1956.

32. Keusch GT: Fever: To be or not to be. *NY State J Med* 76:1998-2001, 1976.

33. Stern RC: Pathophysiologic basis for symptomatic treatment of fever. *Pediatrics* 59:92-97, 1977.

34. Hughes JG: *Synopsis of Pediatrics*, ed 4. St Louis, CV Mosby Co, 1975.

35. Kempe CH, Silver HK, O'Brien D (eds): *Current Pediatric Diagnosis and Treatment*, ed 5. Los Altos, Calif, Lange Medical Publications, 1978.

36. Rudolph AM (ed): *Pediatrics*, ed 16. New York, Appleton-Century-Crofts, 1977.

37. Smith CA (ed): *The Critically Ill Child: Diagnosis and Management*, ed 2. Philadelphia, WB Saunders Co, 1977.

38. Smith DW (ed): *Introduction to Clinical Pediatrics*, ed 2. Philadelphia, WB Saunders Co, 1977.

39. Vaughn VC III, McKay RJ: *Nelson's Textbook of Pediatrics*, ed 10. Philadelphia, WB Saunders Co, 1975.

40. Steele RW: Fever, in Shirkey HC (ed): *Pediatric Therapy*, ed 5. St Louis, CV Mosby Co, 1975.

41. Ziai MA (ed): *Pediatrics*, ed 2. Boston, Little Brown & Co, 1975.

42. MacKinney LG: Fever, in Green M, Haggerty RJ (eds): *Ambulatory Pediatrics.* Philadelphia, WB Saunders Co, 1968.

43. Pizzo PP: Fever, in Graef JW, Cone TE (eds): *Manual of Pediatric Therapeutics.* Boston, Little Brown & Co, 1974, p 175.

44. Steele RW, Young FSH, Bass JW, et al: Oral antipyretic therapy. *Am J Dis Child* 123:204-206, 1972.

Neurofibromatosis With Congenital Glaucoma and Buphthalmos in a Newborn

Leon Satran, MD; Robert D. Letson, MD; Edward L. Seljeskog, MD

• **A newborn infant with unilateral eyelid swelling, proptosis, and glaucoma is described. The diagnosis of congenital neurofibromatosis was made on the basis of a positive family history and by inspection of the patient. It is suggested that this clinical problem is more common at birth than generally recognized. Clinicians should be aware that congenital glaucoma secondary to neurofibromatosis is a distinct entity that can manifest itself in the newborn period.**

(*Am J Dis Child* 134:182-183, 1980)

Neurofibromatosis is a well-recognized problem in infancy and childhood and exhibits great variability in its clinical manifestations.[1,2] Reports of congenital glaucoma in newborns secondary to neurofibromatosis are extremely rare[3,4] and, to our knowledge, have not been presented in the American literature. This case is being described in an attempt to raise the level of awareness of this condition among clinicians.

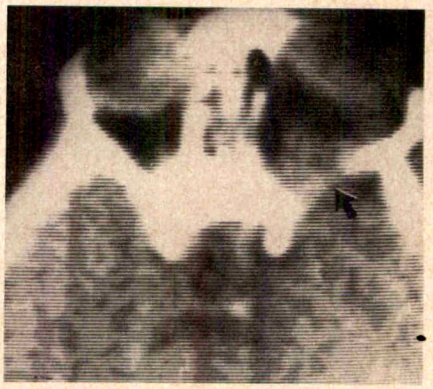
Report of a Case

A 3-week-old female infant was admitted to the University of Minnesota Hospitals, Minneapolis, with a history of swelling of the right eye and upper lid since birth. She was born weighing 2,650 g to a primigravida after an uncomplicated 39-week pregnancy. While in the nursery, haziness of the right cornea and swelling of the right upper eyelid were noted. two weeks later, she was seen by a physician who diagnosed her problem as glaucoma and treatment was begun with 1% pilocarpine hydrochloride solution.

The patient's mother and aunt, who are twins, have neurofibromatosis; the mother also has cafe-au-lait spots, scoliosis, and multiple subcutaneous tumors. Examination of the infant showed a maculopapular rash over the scalp, thought to be seborrheic dermatitis. There was notable exophthalmos and buphthalmos of the right eye. Roentgenograms showed normal optic foramina. An intravenous pyelogram was normal. Further examination of the right eye showed an enlarged, cloudy cornea measuring 12 mm in diameter. The left corneal diameter was 9.5 mm. The lateral portion of the right upper eyelid was floppy, suggesting the presence of an early plexiform fibroma. The intraocular pressure in the right eye was substantially elevated, measuring 35 mm Hg. Pressure in the left eye was not initially measured; but subsequently, under anesthesia, it was found to be within normal limits at 10 mm Hg. Gonioscopy showed open angles bilaterally. On funduscopic examination, a large vascular hemangiomatous lesion was seen in the periphery of the right eye. The right optic disc was normal in color, but the cup-disc ratio of 0.5 (normal < 0.3) indicated a glaucomatous condition, especially

Fig 1.—Notable enlargement of right eye in patient with congenital glaucoma and neurofibromatosis.

Fig 2.—Computerized tomographic study showing mass in apex of right orbit. Proptosis is present, and bony defect in greater wing of sphenoid is indicated by arrow.



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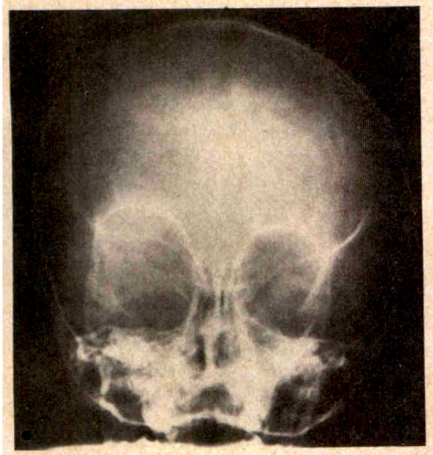

Fig 3.—Notable orbital asymmetry, with right orbit considerably larger than left.

in view of the normal left optic disc, which showed no cupping. Because of the elevated intraocular pressure, enlarged cloudy cornea, and glaucomatous optic cupping, treatment was begun with 4% pilocarpine, 1% epinephrine hydrochloride, and acetazolamide. She was discharged at 4 weeks of age, with a diagnosis of congenital glaucoma secondary to neurofibromatosis.

She was hospitalized for further evaluation at 10 months of age. Results of the physical examination were normal except for the presence of five cafe-au-lait spots distributed on her back and right leg and for notable proptosis of the right eye (Fig 1). Roentgenograms showed progressive enlargement of the right foramen and right superior orbital fissure consistent with the presence of an optic mass. A pneumoencephalogram showed no gross abnormalities, but visualization was incomplete and the presence of an optic mass could not be excluded.

At 27 months of age, a computerized tomographic study showed a mass lesion in the posterior aspect of the right orbit that extended beyond the confines of the optic nerve (Fig 2). At 31 months of age, skull roentgenograms showed an enlarged, deformed right orbit (Fig 3). Surgical exploration showed a plexiform neurofibroma involving most of the right orbit, including the globe, superior rectus and levator muscles, and retrobulbar area. It was decided that removal of the tumor would require complete orbital exenteration; and because of the presence of some vision in the affected eye, such a procedure was not considered at that time. At 44 months of age, vision in the right eye was noted to be minimal. Surgical removal was considered for the future when orbital growth would be more complete and she could more easily be fitted with a prosthesis. At 4 years, 9 months, of age, the right eye was still glaucomatous with only minimal vision present (3/200). Her growth and development were normal as were the results of her physical examination, except for the obvious deformity of the right eye and the cafe-au-lait spots. She is currently being treated with 1% epinephrine.

Comment

Congenital glaucoma may be associated with a variety of systemic disorders such as neurofibromatosis, Sturge-Weber syndrome (nevus flammeus with glaucoma), and Lowe's syndrome (glaucoma associated with cataract, mental deficiency, muscular dystrophy, and renal disease).[5] Increased intraocular pressure usually becomes apparent in the first year of life. Presumably, the mode of pathogenesis for glaucoma is obstruction of the aqueous humor outflow channels by the presence of an intraocular mass. When the intraocular pressure is increased in an infant, the elastic outer coats of the eye distend, leading to an enlarged eye. The descriptive term "buphthalmos" has generally been applied to such an eye. The rarity of the condition increases the likelihood of missing the diagnosis in the early stages.[6]

Although the first clinical signs of neurofibromatosis are usually multiple cafe-au-lait spots,[1] ocular signs may predominate to such an extent that the problem can freqently be recognized by simple inspection of the child in combination with a positive family history. Definitive diagnosis most commonly occurs when parents recognize a growing mass that leads them to seek medical attention.

Glaucoma in newborn infants secondary to neurofibromatosis undoubtedly exists more than is generally recognized. It is usually, however, only after several weeks or months, when the infant's affected eye has enlarged to a point where the condition is obvious, that the diagnosis is more readily made. We would urge that this clinical problem be considered when encountering small infants, even as newborns, with eye abnormalities and family histories similar to those described in this report.

Richard Latchaw, MD, of the Department of Radiology at the University of Minnesota, Minneapolis, prepared the illustration of the computerized tomographic study.

References

1. Fienman NL, Yakovac WC: Neurofibromatosis in childhood. *J Pediatr* 76:339-346, 1970.

2. Chalhub EG: Neurocutaneous syndromes in children. *Pediatr Clin North Am* 23:505-509, 1976.

3. Pestre A: Syndrome de Recklinghausen et buphtalmic glaucomateuse chez un nouveau-né. *Bull Soc Ophtalmol Fr* 71:1034-1038, 1971.

4. Payeur MG, Rey-Goetz ML, Beauvais P, et al: Un cas de maladie de Von Recklinghausen congenitale avec glaucome. *Bull Soc Ophtalmol Fr* 76:177-179, 1976.

5. Bettman JW, Cleasby GW: Congenital glaucoma. *Pediatr* 32:420-424, 1963.

6. Shaffer RN: Congenital glaucoma. *Int Ophthalmol Clin* 3:107-116, 1963.

Review

Bacterial Immunizations

H. Robert Harrison, PhD, MD, MPH, Vincent A. Fulginiti, MD

In the past two decades, viral vaccines have captured the interest and imagination of scientist and practitioner. The elimination of smallpox and the potential control of polio, measles, and other childhood diseases have overshadowed the slower progress with bacterial vaccines. This review will place bacterial vaccines in perspective and outline theoretical and practical aspects of their development and usage.

HISTORY

Bacterial "vaccinology" does not have an historic origin analogous to Jennerian vaccination. The first scientific attempt was Pasteur's experiments with veterinary diseases.[1] Aged cultures of attenuated fowl cholera and anthrax bacilli were used to immunize susceptible animals. In both instances, these animals became remarkably resistant to challenge by virulent organisms. In parallel, and in sequence, others explored the use of killed and attenuated bacteria in the prevention of human disease. Koch discovered cell-mediated immunity during a search for tuberculosis vaccine. Von Behring and Kitasato discovered diphtheria antitoxin and passive immunity during primitive studies of diphtheria immunization.

The first generally used bacterial vaccine for man was a type of typhoid vaccine.[2] In 1884, Solomon and Smith demonstrated that heat-killed hog cholera baccillus (a salmonella) protected pigeons against virulent challenge. Pfieffer and Cole immunized two humans in 1896 with heat-killed typhoid bacilli. Almrath Wright drew on these two events to develop an effective typhoid vaccine in 1898.

At the time, typhoid was more devastating than war. It killed 5,000 each year in England and 35,000 each year in the United States. The case-fatality rate ranged from 10% to 30%; seven times as many soldiers died from typhoid as did from battle injuries in the Spanish-American War.

Wright systematically tested a heat-killed typhoid vaccine until 4,000 Indian Army volunteers had received it. Reactions to the vaccine were severe, but protection was striking; mortality decreased from 14% to 2%. Despite problems with politics and excessive vaccine reactivity, additional large-scale studies were carried out during World War I. Among 1,125,000 immunized British troops, only 7,500 cases of typhoid occurred, with 266 deaths. In contrast, during the South African war, 73,633 unimmunized soldiers contracted typhoid and 10,144 died.

This early success encouraged others to explore the use of cholera and plague vaccines and opened the door to modern bacterial vaccinology. Reactions to all of the bacterial vaccines were severe, but protection against disease was striking. Despite the reactions and despite technological accidents yielding virulent or contaminated vaccines, progress in development continued, culminating in vaccines against diphtheria, tetanus, pertussis, and other bacterial diseases. For a full review of this fascinating era in microbiology and medical and human history, the reader may consult the references by Parish.[1,2]

THE IMMUNOLOGY OF BACTERIAL INFECTION

Despite broad advances in the science of immunology, our knowledge of bacterial immunity is primitive in some areas, and only modestly sophisticated in others. This section explores what is known of bacterial immunity and its relationship to vaccines, sera, and γ-globulin.

Bacterial Infection: Pathogenesis

Bacteria produce disease[3,4] directly by invasion or indirectly through the elaboration of substances injurious to the host. Virulence of a specific organism is related to its capacity to establish itself, penetrate tissue, or produce toxins, enzymes, etc.

To successfully infect a host, a sufficient quantity of bacteria must find access to fertile sites in the host that provide nutrients for replication and that are not inimical to bacterial survival. Having established a locus for replication or metabolic activity, the bacteria can then produce disease by direct tissue injury or indirect effects. Invasiveness is an important characteristic of some virulent bacteria. If, in addition, the organism has survival mechanisms that rebuff human defense systems and elaborates elements destructive to cells, systemic

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disease and metastatic infection results.

Salmonellae provide a model for these attributes. A sufficient infective dose must be ingested or no infection is established. Some salmonellae have high potential for invasion (*Salmonella typhi*) and produce bacteremia with little or no gastrointestinal (GI) disturbance. Others are virtually noninvasive, producing most of their effects locally in the intestine, with resultant gastroenteritis.

• Specific bacterial metabolic products influence survival of the bacteria. Toxin production often damages tissue, resulting in favorable circumstances for growth. Enzymes may allow bacterial penetration deeper into tissues, with spread and replication. Successful survival in the blood results in dissemination and organ-specific infection.

Host Responses

The array of responses[4] to bacteria are numerous and varied. Most nonspecific responses will not be extensively considered here, but it must be remembered that they contribute heavily to prevention of bacterial colonization and local growth.

Nonspecific Mechanisms

The only nonspecific factors of importance to our discussion are the phagocytic cells and chemical substances that interact with bacteria and phagocytes. The reticuloendothelial system has the capacity to ingest and destroy bacteria. Circulating phagocytes, wandering tissue macrophages, and fixed tissue phagocytes all play a role. Random contact occurs in the absence of specific immunity; phagocytosis is enhanced by naturally occurring opsonins. This primitive defense system is limited in its effectiveness, and the host depends on specific immunity to facilitate bacterial elimination and control.

Specific Immunity

There are two elements of specific immunity involved in bacterial defense: antibody-mediated and cell-mediated immunity.

Antibody Immunity.—Antibody synthesis is stimulated by antigenic structures on the surface of bacteria, by substances elaborated by the bacterium, or by internal structures made available during bacterial disintegration. In general, IgM is produced first; and in the normal sequence, it gives way to IgG antibody, which becomes the principal immunoglobulin involved in antibody activity.

IgM seems to be a more primitive response both phylogenetically (it develops first in lower species) and ontogenetically (it is the first immunoglobulin produced by the human fetus). It is a more efficient mediator of opsonization than IgG, rendering the bacterium more susceptible to phagocytosis. Since the earliest contact after infection is between bacteria and phagocytic cells, the early presence of IgM-antibody seems to facilitate this control mechanism. IgM is also more efficient than IgG in killing bacteria and in agglutinating them. On the other hand, IgG antibody functions best in precipitation, thus dealing efficiently with chemical products of bacteria. Neutralization of toxin, enzymes, and other bacterial products further counters the virulence of bacteria, aiding in their elimination.

Finally, IgA production may be stimulated and provides effective barrier functions at mucosal surfaces. Many bacteria are relatively or absolutely noninvasive but possess powerful exotoxins that cause disease. Control of these organisms involves secretory IgA present in high concentration on endothelial surfaces as well as local inflammation and leakage of plasma IgM, IgG, and cellular elements.

All of the aforementioned events describe the initial encounter between bacterium and host; subsequent contact rapidly calls forth IgG (and possibly IgA) antibodies that may prevent even the initial virulence of organisms by containing their growth in the GI or respiratory tract and by neutralizing elaborated noxious substances. This anamnestic response can result in no infection on second contact or the limitation of infection to trivial disease. Thus, inhaled pneumococci may be attacked by specific secretory IgA previously stimulated. If lymphatic or bloodstream invasion occurs, rapid control may be achieved by preexistent and readily recalled specific IgG antibody. The child may experience no disease or mild respiratory symptoms instead of pneumonia and bacteremia.

Cell-Mediated Immunity (CMI).—Much less is known of the role and importance of CMI in recovery from and resistance to bacterial infection. The bacterial model most often cited is tuberculosis, in which CMI is readily demonstrable and related to pathogenesis, recovery, and immunity. For more common bacteria, there is less information although a body of data is growing that suggests that CMI responses to bacteria do occur.

RECAPITULATION

Bacterial contact calls forth an array of nonspecific and specific defenses on the part of the host. Outcome of bacterial-host contact is dependent on the efficiency, specificity, and speed of these responses balanced against the virulence of the bacterium. In normal individuals, most encounters result in trivial or no disease; only rarely does clinical symptomatology of an important degree occur, and even less commonly does the host die. Individuals who lack individual components of the defense system are susceptible to serious, persistent, recurrent, and even lethal infections dependent on the degree and specificity of the defect and the chance encounter with appropriate bacteria.

IMMUNIZATION AGAINST BACTERIAL INFECTIONS

General Principles

Effective vaccines are dependent, in part, on precise knowledge of natural immunity. Often, the degree of protection afforded by a given vaccine parallels our insight into the pathogenesis of disease and host defenses. For example, knowledge that tetanus is produced solely by the effects of an exotoxin of *Clostridium tetani* enables us to use vaccine that evokes antitoxin rather than one directed at the whole organism. Further, exogenous antitoxin can be used in prevention and treatment. On the other

hand, little is known of pertussis immunity, with the result that a crude vaccine is used that provides only 75% to 85% protection and includes many bacterial components that are both harmful to the host and of unknown immunologic benefit. Further, pertussis immune globulin seems of no benefit in either prevention or treatment.

All available bacterial vaccines are given by injection, a method that bypasses the natural mode of infection. This results in a disparity between stimulation of systemic immunity and topical immunity; the latter does not develop and this limits the vaccine's effectiveness in control of initial stages of infection. Current investigative interest focuses on mimicry of the normal route of infection, with the anticipation of improved protection.

SPECIFIC VACCINES

Diphtheria

Principles of Immunity.—*Corynebacterium diphtheriae* produces disease by the establishment of a focus of infection (respiratory tract or skin) and the elaboration of a potent exotoxin. The exotoxin is destructive to all cells, but myocarditis, tubular necrosis, and myelin degeneration are most obvious in the human.[5] Free toxin and that attached to cell-surface receptors can be neutralized by antitoxin; intracellular toxin is not affected. Establishment of infection is partially dependent on the organism's capacity to produce toxin; this results in local tissue destruction allowing survival and growth of the bacterium.

Preexisting antitoxin in the human results in little systemic disease; that which occurs is mild and nonlethal.[6] Administration of antitoxin to a person already infected controls further development of toxin-induced effects and neutralizes some of the toxin already circulating and present on cell surfaces. Routine, active immunization practice is aimed at immunizing all individuals early in life and at sustaining immunity by periodic additional doses of vaccine.[7]

Vaccines Available.—Diphtheria toxoid is prepared singly or in combination with other antigens.[8] It is formaldehyde-inactivated toxin produced by the PW-8 strain. It also is manufactured as a fluid preparation and as an adjuvant vaccine containing alum. The fluid vaccine has no true advantages and will not be further considered.

A single dose of 0.5 mL of any of the vaccines contains sufficient toxin to be immunogenic. Full immunologic response occurs only with a complete primary series and a booster one year later.[9] Subsequent immunity is maintained by periodic booster doses as outlined in the text. The goal is to maintain circulating antitoxin levels at 0.02 unit/mL of serum or higher.

Diphtheria toxoid, adsorbed.—It contains 7 to 25 IU of toxoid in 0.5 mL of vaccine.

DT (Pediatric) Diphtheria-Tetanus Toxoids, Adsorbed.—This contains 7 to 25 IU of diphtheria toxoid and tetanus toxoid. It is for use only in children less than 7 years old.

Td (Adult) Tetanus-Diphtheria Toxoids, Adsorbed.—This contains full amounts of tetanus toxoid plus not more than 2 IU of diphtheria toxoid. This is for use in primary and booster immunization in anyone 7 years of age or older.

Diphtheria-Tetanus-Pertussis (DTP).—This contains full doses of diphtheria and tetanus toxoid plus pertussis vaccine. It is intended only for immunization of infants and young children.

Schedules.—Diphtheria immunization is ordinarily accomplished as DTP immunization at 2, 4, 6, and 18 months of age.[10] Another booster is given at school entry and every ten years thereafter as Td. The reduction in diphtheria toxoid concentration in Td boosters is mandated by the high reactogenicity of toxoid in older individuals.

For individuals unimmunized in infancy but less than 7 years of age, TD (DT, pediatric) may be substituted for DTP in the same schedule. For unimmunized individuals older than seven years, three doses of Td with a booster one year later and every ten years thereafter suffices.

Immunized close contacts of patients with clinical diphtheria should receive a booster dose of the appropriate vaccine for their age. Unimmunized contacts can be immediately protected by antitoxin plus antibiotics with concurrent immunization, with special attention to booster doses to insure immunity.[11] Recovery from clinical diphtheria does not confer immunity; immunize patient as appropriate for age.

Side Effects and Adverse Reactions.—The usual use of multiple antigen vaccines makes evaluation of the side effects of diphtheria toxoid difficult. Much of our information derives from earlier experiences when this vaccine was used singly and fails to account for recent technological changes in the preparation and purification of toxoids.

Local tenderness, erythema, and induration occur in as many as 54% of recipients.[12] Serious side effects are uncommon in infants and children; they are more frequent among adults. For this reason, DT is used in individuals less than 7 years old and Td in those older than 7 years. Rare reports of isolated instances of hypersensivity have been recorded.

Tetanus

The etiologic agent of tetanus is *Cl tetani*, which is an anaerobic, spore-forming, Gram-positive rod; it exists in nature as an extremely resistant spore. It is introduced into an area of injury in that form; within the wound, the conversion from spore to the toxin-producing vegetative organism is dependent on a host of local factors.[13,14] All the clinical features of tetanus are produced by the activity of the soluble exotoxin, tetanospasmin,[15] which is produced by the vegetative form of *Cl tetani*; the organism itself causes no disease.

Principles of Immunity.—There is no natural immunity to tetanus.[16] Immunization strategy uses the observation that clinical immunity depends on the presence of circulating antibody against tetanospasmin. Thus, prophylaxis is achieved with either active stimulation of antibody, passive antibody transfer, or a combination of both. The basis for active immunization is formaldehyde denatured tetanospasmin (tetanus toxoid), which is antigenic but nontoxic. Production of

antibodies to the toxoid renders the patient immune to tetanospasmin.[17]

Vaccines Available.—Tetanus toxoid is available as an aluminum phosphate adsorbed or a fluid vaccine. The fluid toxoid has been used only for booster doses when rapid protection is required,[13] but it induces an antibody response of a much shorter duration.[10] Adsorbed vaccine (and not the fluid form) is antigenic in the presence of passively received antibody[18] and is the only preparation recommended for primary immunization.

Aluminum phosphate adsorbed tetanus toxoid is available as the following: triple antigen (diphtheria-tetanus-pertussis, DTP); diphtheria and tetanus toxoids, adsorbed, pediatric (DT); and tetanus and diphtheria toxoids, adsorbed, adult type (Td). Td contains a smaller dose of diphtheria than DT and is used in those younger than 7 years old for recall and in adults not previously immunized.

Schedules.—Three vaccine schedules have been designed.

Routine Immunization.—Children 2 months to 7 years of age should be given three DTP immunizations intramuscularly at six to eight week intervals, with a fourth injection one year after the third dose.

Children More Than 7 Years Old and Adults Not Previously Immunized.—Two doses of Td vaccine should be given intramuscularly two months apart, with a third dose given six to 12 months later. It should be noted that the first dose of vaccine produces little or no increase in antibody titer. Antibody levels increase after the second and subsequent doses. The accepted protective level of circulating toxoid antibody is 0.01 unit/mL.

Booster Doses.—The decay rate of endogenous tetanus antitoxin is low in both children and adults.[19] There is also a strong correlation between the occurrence of reactions to booster doses and the patient's circulating tetanus antitoxin levels. To minimize both acute hypersensitivity and Arthus-type reactions, it is recommended that booster doses be given intramuscularly every ten years. If a dose is administered sooner as part of wound management, the next routine booster is given ten years from that time.

Side Effects and Adverse Reactions.—Local and systemic reactions to tetanus toxoid are uncommon in children.[17] These can be categorized as urticarial, with or without angioneurotic edema and not necessarily limited to the site of injection, and as Arthus type (the most common). Rarely, delayed-hypersensitivity reactions may occur. Evidence now suggests that too many injections may lead to a qualitative change in the spectrum of antibodies produced, with an increasing frequency of those of reaginic type.[20]

Pertussis

Principles of Immunity.—We do not know why children recover from pertussis nor which antigens evoke which immunologic responses related to protection.[21] Although much is known of the antigenic composition of *Bordatella pertussis* and some information is available on specific antibody responses, no conclusive and noncontroversial link between immunity and protection has been made.

Antibodies of various types have been described after natural infection and immunization in animals and man.[21] No one class of antibodies nor one type of specific antibody action seems to correlate perfectly with recovery and immunity. Studies of cell-mediated immunity and topical respiratory immune mechanisms are still preliminary and have shed little light on this critical issue.

Thus, we still immunize against pertussis without much information. The best-performed studies here and abroad demonstrate efficacy for whole-bacterial pertussis vaccines, which are partially contingent on the specific serotypes included and the potency of the particular preparation.[22]

No other vaccine has evoked as much controversy concerning its efficacy vs its side effects and adverse reactions. Even today in England, there are some scientists and practitioners who doubt that pertussis vaccine affords sufficient protection to use it positively in the light of its predictable adverse consequences.[23] An exhaustive review of all the data and arguments is not indicated here.

We conclude that pertussis vaccines as used in the United States offer protection against the disease.[24] This protection is limited in quantity (75% to 85% reduction in the incidence of pertussis in those fully immunized as opposed to unimmunized children) and in duration (immunity wanes after the primary series and boosters). Pertussis can be a devastating disease, especially in the very young; and even this degree of protection is desirable. Adverse effects will be considered later, but they further limit the value of current vaccine usage and indicate the need for development of new vaccines.

Obviously, the need is for more precise definition of specific immunity and for design of a vaccine that yields maximum protection at little or no risk. Such efforts are underway, with components of the organism as the primary antigen.

Vaccines Available.—Pertussis vaccine can be administered alone or in combination with diphtheria and tetanus toxoids. It is available as a plain preparation or adsorbed to alum. The adjuvant vaccine contains 4 protective units/0.5 mL dose whereas the plain vaccine contains somewhat more antigen. There is no rationale for the use of plain pertussis vaccine; it offers no immunologic advantage nor is it safer. All pertussis vaccines whether alone or in combination with other antigens contain whole bacteria that have been inactivated.

Plain Pertussis Vaccine (Without Alum).—It is useful in epidemics for rapid protection. Administer three intramuscular (IM) doses of 0.5 mL (4 National Institutes of Health [NIH] units) each, at monthly intervals.

Adjuvant Pertussis Vaccine (With Alum, Aluminum Phosphate, or Aluminum Hydroxide).—Give three IM doses of 0.5 mL (4 NIH units) each, at monthly intervals, for primary immunization. Within eight to 12 months after primary immunization, whether with plain or adjuvant pertussis vaccine, a booster dose of adjuvant vaccine should be used.

DTP.—This is a combination of the bacterial suspension of pertussis plus

the two toxoids. It is usually distributed in multiple-dose vials. Give three IM doses of 0.5 mL each, administered at bimonthly intervals. A booster dose should be given at 18 months of age and again at 4 to 5 years.

Schedules.—Pertussis vaccine is designed primarily for use in infancy and early childhood.

Primary Immunization in Infancy.—Pertussis vaccine is usually administered in combination with diphtheria and tetanus toxoid as DTP.[10] Each 0.5-mL dose of DTP contains 4 units of pertussis vaccine.

Three doses of DTP (a total of 12 units of pertussis antigen) are given intramuscularly at two-month intervals beginning at 2 months of age. In areas of high endemicity or during epidemics, it may be desirable to start immunization earlier. The vaccination is begun at 4 to 6 weeks of age, and three doses one month apart are given. Rarely, in severe epidemics affecting extremely young infants, pertussis immunization can be started in the first few days or weeks of life, but this is seldom necessary. After primary immunization, a booster is given one year later.

Recall Immunization.—Routine recall boosters are suggested when the child enters school. If pertussis is prevalent in adolescence, a half dose can be given to children older than age 7 years and to adults requiring booster doses.

Special Circumstances.—After intimate exposure to pertussis or during epidemics, children younger than 7 year of age can receive a 0.5-mL dose, and older patients should receive 0.25 mL of either DTP or pertussis adsorbed vaccine, depending on age.

In children with neurologic diseases, one wishes to protect against pertussis but also to avoid the toxicity of pertussis vaccine on the CNS. Most experts advise using pertussis adsorbed vaccine alone and dividing the needed 12 units among several small doses. One such regimen would be to use 0.1 mL (approximately 1 protective unit) given monthly until all protective units are administered. Others divide a 0.5-mL dose in half, for six injections. Many experts suggest that unchanging neurologic disease in infancy is not a contraindication to full doses and the usual schedule of pertussis immunization that developers advocate. If, for example, the child has congenital hydrocephalus without convulsive disorder or without a changing pattern of neurologic deficit, it would be perfectly alright and even desirable to proceed with the pertussis immunization at the usual time with the usual doses and the usual vaccine. On the other hand, if a child has a convulsive disorder or a changing encephalodegenerative disease, it would be unwise to attempt any pertussis immunization at all. Although fractional doses are widely used for children and infants with neurologic disease, we believe it is neither necessary nor desirable.

In children with previous reaction to pertussis vaccine that are of severe systemic or CNS character, *no further pertussis vaccine should be given.* If the reaction has been local or systemic of mild degree, pertussis vaccine can be separated from DTP and the aforementioned procedure followed. On the other hand, many practitioners will give full doses of DTP in these circumstances. There is no evidence that reactions will increase in severity with subsequent doses. However, it is important to emphasize that when any CNS symptoms follow the administration pertussis vaccine, further pertussis vaccine should not be administered.

Side Effects and Adverse Effects of Immunization.—Both local and systemic adverse effects may occur with pertussis vaccine.[12,22,25-27] Local reactions consisting of pain, induration, and redness may occur in as many as 70% of recipients. Occasionally, a sterile abscess may develop at the injection site; but with modern, careful aseptic technique, this is a rare event.

Mild systemic symptoms are also frequent after pertussis immunization. Low-grade fever, irritability, feeding difficulties, and excessive sleepiness have all been reported. More severe reactions consisting of high temperature alone (greater than 40 °C) are encountered in 1% to 5% of pertussis vaccine recipients.

Convulsions, with and without fever, have been encountered with variable frequency after pertussis immunization. Recent data suggest that the incidence is 1/1,000 to 2,000 immunizations. Others have estimated less common frequencies in the range of 1/3,000 to 50,000 immunizations. As many as 50% to 80% of patients with convulsions will also have fever. It is difficult to be certain of the relationship between fever and the convulsive episode.

Children with a history of convulsions are extremely likely to have convulsions at the start of pertussis immunization. Children who react to pertussis vaccine with a convulsive episode probably have an even greater risk of convulsion after subsequent immunization. The difficulty of all statistical evidence of convulsions in association with pertussis vaccine is the background incidence of convulsions in the age group that receives DTP. As many as 1% of children in this age group may have convulsions unassociated with pertussis immunization. However, there seems to be little question that pertussis immunization does increase the frequency above this background rate and that in the aggregate it is responsible for convulsive episodes. A more serious complication of pertussis vaccine is the encephalopathy syndrome. Clinical manifestations range from sudden collapse through persistent screaming to frank neurologic degenerative disease and even death. Sudden collapse may be due to a shock-like syndrome possibly associated with acute anaphylaxis or may be a manifestation of acute encephalitis. The "persistent crying" syndrome has been anecdotally described for a number of years; more recently, a comprehensive study in Los Angeles by L. Baraff, MD, and J. Cherry, MD (unpublished data, 1977 to 1979) suggested that persistent crying may be secondary to CNS irritation. As many as 5% of their DTP recipients had persistent crying and 0.2% had collapse. Others have reported an even higher incidence of these reactions.

The estimates of frank encephalopathy after pertussis vaccines have ranged from as many as 1/6,000 doses to as few as 1/1,000,000 doses.[25-28]

Many experts are of the opinion that an incidence of 1/50,000 to 100,000 is the most likely reaction rate in the United States. As of this writing, the precise incidence is unknown.

The outcome of encephalopathy syndromes may range from almost an immediate recovery through residual neurologic damage of varying degree to death. One British study concludes that the risk of residual brain damage from pertussis immunization is 1/300,00 immunizations. Once again, difficulty in ascribing a particular encephalitic reaction to pertussis immunization is highlighted by nonpertussis encephalitic syndromes occurring in the age group receiving vaccine. Less commonly encountered reactions after pertussis immunization are acute anaphylaxis and postimmunization thrombocytopenia.

Pneumococcus

Principles of Immunity.—The pneumococcus (*Streptococcus pneumoniae*) depends for its pathogenicity on a polysaccharide capsule that renders it resistant to phagocytosis and destruction. The human host, in turn, responds to infection with production of antibody to this polysaccharide capsule. Recovery from pneumococcal infection is associated with the presence of antibody to the capsular polysaccharide. Immunity is type specific: antibody is directed against only the polysaccharide of the invading organism, and it is ineffective against the other 83, or more, known types of pneumococci.

Vaccines Available.—Vaccination with purified combined pneumococcal polysaccharide antigens has been demonstrated to elicit antibody and protect against natural disease from organisms of the capsular types included in the vaccine.[29,30] Indeed, a combined polysaccharide vaccine similar to the currently available one was licensed and produced in this country from 1945 to 1947. However, the availability of effective antibiotics against the pneumococcus led to the discontinuation of vaccine production.

The continuing high mortality from pneumococcal disease despite appropriate treatment, plus the emergence of resistant pneumococci, has led to a revival of interest in pneumococcal vaccine. The 14-valent polysaccharide vaccine now available contains, per 5-mL dose, 50 μg of purified capsular polysaccharide for each of the 14 serotypes (American types 1, 2, 3, 4, 6, 8, 9, 12, 14, 19, 23, 25, 51, and 56) causing at least 80% of serious pneumococcal disease in the United States.[31] The carrier is isotonic saline solution containing 0.25% phenol as a preservative.

Schedules of Immunization.—Although experience with the polyvalent vaccine in adults has been highly favorable, there is limited information for children. So far, studies of children indicate that those less than 2 years of age exhibit unsatisfactory serologic responses to a single dose of vaccine.[32] No booster effect has been seen so far in adults, and the effect of a booster in children is unknown. In a small group of children older than 2 years with sickle cell anemia and splenectomy, the incidence of bacteremic pneumococcal disease seemed to be reduced after immunization with a single dose of an 8-valent vaccine.[33]

The data currently available permit the vaccine to be recommended for use in children older than *2 years of age* who are at risk for severe or life-threatening pneumococcal disease. These include children with sickle cell anemia, those with splenectomy,[34] and perhaps those with Hodgkin's disease, prior to splenectomy or treatment.[34] In addition, children with nephrotic syndrome should be considered as candidates for inoculation.[35] In all cases, a single 0.5-mL dose given subcutaneously or intramuscularly is recommended. This recommendation may change with continuing experience with children.

Side Effects and Adverse Reactions.—Children who receive the vaccine may experience pain, erythema, and induration at the site of injection. A small number may have a slight temperature elevation. No substantial reactions have been noted.

More recent experience indicated that children and adults who have received pneumococcal vaccine may experience severe and even fatal bacteremia with pneumococci included in the vaccine grouping as well as among those strains not included.[36] Those infections that have occurred with strains included in the vaccine seem to occur because the recipient does not respond adequately to that particular antigen. Of course, those infections occurring with strains not included in the vaccine could not have been prevented. The practical meaning of these new data are that children who receive pneumococcal polysaccharide remain susceptible to bacteremia and therefore must receive ongoing prophylaxis and prompt, vigorous therapy of any infectious episode. In general, this means continuous ampicillin sodium therapy for children less than 4 years of age and penicillin prophylaxis for children older than 4 years. One should also remember that asplenic children may experience infection with organisms other than the pneumococcus, thus each infectious episode should be treated as potentially bacteremic and lethal.

Meningococcus

Principles of Immunity.—Circulating antibodies to meningococcal cell-surface antigens constitute a major defense against systemic meningococcal disease.[37,38] In the last ten years, there has been an attempt to protect humans from meningococcal disease through the use of active immunization with group-specific purified capsular polysaccharide vaccines. Numerous large-scale studies have shown that in adults and older children, group A and group C vaccines can prevent infection with meningococci of these serotypes.[39-41] The group B polysaccharide is poorly immunogenic,[42] so that efforts with group B prophylaxis are being directed at a vaccine based on protein rather than polysaccharide components of this organism.[43]

More than two-thirds of all meningococcal disease occurs in people younger than 20 years old.[44] Group A infections are uncommon in this country; group B and C have their highest age-specific attack rates in infants and young children. In recent years, disease in civilians has occurred primarily as isolated cases or, occasionally, as small clusters. Secondary cases occur preponderantly in household contacts.[44]

Vaccines Available.—Two meningococcal polysaccharide vaccines, monovalent A, and monovalent C, are of importance. Each monovalent dose contains 50 μg of a freeze-dried, group-specific purified polysaccharide (polymers of particular neuraminic acids) that is reconstituted with isotonic saline solution containing 1:10,000 thimerosal as a preservative. The injection is given subcutaneously.

Schedules and Indications.—There is much debate about the usefulness of meningococcal vaccines in pediatric practice. They are expensive, relatively ineffective in young children, and the duration of clinical immunity conferred is still unclear. Recent evidence suggested that most infants older than 12 months of age will have protective levels (2 μg/mL) of antibody develop after a dose of monovalent A vaccine.[45] Clinical immunity seems to last at least two years. Although group C vaccine has been used successfully in military recruits, children younger than 6 years old show a variable response, with many, especially those younger than 2 years, achieving nonprotective antibody levels.

In our country, meningococcal disease is uncommon, and it occurs primarily in the extremely young, in whom the vaccines are least effective. Vaccination should be offered to military recruits, to hospital personnel regularly, and to household contacts (older than 1 year of age) of patients with the disease.[44,46] In addition, some form of antimicrobial prophylaxis (rifampin is recommended) should be given these contacts during the brief period (approximately five days) before immunity develops. Serogroup-specific vaccine may also be used to control a community outbreak caused by group A or C meningococcus.

In areas where meningococcal outbreaks are common, such as parts of Africa, a much stronger case for routine immunization can be made. However, that discussion is outside the scope of this article. Travelers from the United States to endemic areas of group A and C disease may benefit from immunization.

Side Effects and Adverse Reactions.—Adverse reactions are infrequent and mild, consisting of localized erythema, pain, and induration lasting one to two days.

Cholera

Principles of Immunity.—Cholera is caused by *Vibrio cholerae* and results in a devastating fluid-loss diarrhea. Immunity to the disease probably results from secretory mechanisms, possibly secretory IgA-specific antibody, at the intestinal level. Thus, the results of parenteral administration of cholera vaccine are understandably disappointing.[47] Only 60% to 80% protection is afforded, for short periods, often less than six months.

Vaccines Available.—Current vaccine consists of a combination of several strains of phenol-inactivated *Vibrio* whole bacterial cells. It is administered subcutaneously or intramuscularly.

Schedules of Immunization.—*Only children older than 6 months should receive the vaccines.* Primary immunization consists of two doses of vaccine (intramuscularly or subcutaneously) given one week to one month or more apart. Specific dose for age is: 6 months to 4 years, 0.2 mL; 5 to 10 years, 0.3 mL; 10 years and older, 0.5 mL. An identical dose is given as a booster six months later.

For children older than 5 years of age, some prefer the intradermal route to minimize reactions; the intradermal dose is 0.2 mL for both primary and booster doses.

Side Effects and Adverse Reactions.—Tenderness, erythema, and induration for one to two days postimmunization are frequent. In some individuals, fever, malaise, and headache also occur; they are occasionally severe enough to require bed rest for short periods. Reactions of all types are less common with intradermal immunization.

Plague Immunization

Principles of Immunity.—Plague is caused by *Yersinia pestis*. Immunity is presumably related to circulating antibody and immunization seems to be of some benefit.[48]

Vaccine Available.—Heat-killed organisms make up plague vaccine. Use of the vaccine is associated with decreased morbidity and mortality.

Schedules of Immunization.—Plague vaccine is reserved for children traveling to or residing in endemic areas who are at high risk of exposure. Primary immunization consists of three IM injections of vaccine: the first two injections at 30-day intervals, and the third four to 12 weeks after the second. Specific dose for age is as follows, with booster dose at 40% of initial dose:

Age, yr	Primary Immunization, mL	Booster, mL
<1	0.1	0.04
1-4	0.2	0.8
5-10	0.3	0.12
≥10	0.5	0.2

Typhoid

Typhoid is caused by systemic infection with *Sal typhi*. Immunity to typhoid does not seem to be related to the presence of antibodies against the usual antigens of *Sal typhi*.[49] The titers of O, H, or Vi antigens are unrelated to resistance to infection. In experimental disease, the macrophage seems to be a major component of resistance to challenge with typhoid bacilli. Antigens of the organisms seem to activate macrophages, enabling them to resist challenges with living virulent organisms. There is some speculation that cell-mediated immunity may play an important role in typhoid resistance and recovery from infection.

Vaccines Available.—Acetone-killed typhoid vaccine is preferred by many and consists of inactivated, whole bacteria and fragments. Acetone-killed typhoid vaccine should not be given intradermally.

Schedules of Immunization.—Typhoid vaccination is no longer recommended routinely for persons living in the United States. Selective immunization is suggested for the following categories: persons with intimate exposure to a documented typhoid carrier; and travelers to epidemic or endemic areas. Typhoid vaccine is not necessary for persons in an area of natural disaster or for those attending such activities as summer camps. The vaccine protects 70% to 90% of recipients against low-dose exposure. Ordi-

narily, protection against ingestion of lightly contaminated materials such as water is achieved, whereas protection in situations where heavily contaminated foodstuffs are involved is usually not obtainable.

Children younger than 10 years of age and older than 6 months of age should receive two 0.5-mL doses subcutaneously, four or more weeks apart. Booster doses should be given at least every three years for continued exposure. Physicians who use nonacetone-killed vaccine often give 0.1 mL intradermally as the second dose for children of all ages. Acetone-killed typhoid vaccine should not be given intradermally.

Side Effects and Adverse Reactions.—Typhoid immunization may cause discomfort at the site of injection, often accompanied by fever, lethargy, headache, and myalgia. On occasion, the reaction is severe enough to require bed rest. Regional lymphadenopathy has also been observed.

Anthrax

The agent of anthrax, *Bacillus anthracis*, is endemic in certain parts of the world. Exposure in this country is primarily an occupational hazard: workers who process hides, hair, bone, wool, and animal product fertilizer; veterinarians; and agricultural workers who handle infected animals are at risk.[50,51] Anthrax is infrequent and sporadic; rare, nonoccupational cases have occurred in home craftsmen working with contaminated yarn. In 1978, six cases of human cutaneous anthrax were reported, four in industrial settings and two in agricultural ones.[52]

Vaccine Available.—The vaccine is a cell-free, alum-precipitated antigen prepared from sterile culture filtrates in which the Rl-NP mutant of the Volum strain of *Bac anthracis* has grown.[53] This mutant is nonproteolytic and unencapsulated.

Schedules of Immunization.—Vaccination is reserved for those at high risk for exposure. An antibody response may be expected in anyone older than 6 months of age. Three subcutaneous doses of 0.5 mL are given at two to three week intervals, with an annual 0.5-mL booster.[54]

Side Effects and Adverse Reactions.—Reactions include local edema, induration, warmth, tenderness, and pruritus, with occasional systemic malaise.[54] Immunization of contacts of cases is unnecessary, and immunization of children would almost never be indicated.

Tuberculosis

Principles of Immunity.—Tuberculosis is caused by *Mycobacterium tuberculosis*. Although the disease has shown a continuous decline during the past century, pockets of infection remain within our population. Tuberculosis is still encountered in children in urban ghetto areas as well as among Native American Indians both on the continent and in Alaska. States bordering on Mexico also encounter instances of tuberculosis in children and in immigrants and migrants from Mexico.

Immunity to tuberculosis is a complex phenomenon but rests primarily on development of cell-mediated immunity, manifest as a delayed hypersensitivity reaction to tuberculin. Long before sophisticated understanding of the immunology of tuberculosis was available, a living attenuated strain of *M bovis* was developed by Calmette and Guérin at the Pasteur Institute in France. It was first utilized in 1921 and has been the source of considerable controversy ever since.[10,55-57]

Vaccines Available.—The official designation BCG is used for strains of vaccine developed from the original isolate of Calmette and Guérin. There are many BCG vaccines available today. They vary in their effectiveness and in the reactions they evoke as well as in their capacity to prevent tuberculosis.

Currently available vaccines in the United States are only distantly related to the original isolate, having undergone additional culture passages and changes in the technology of vaccine preparation and preservation.[58] Current vaccines are freeze dried and are attenuated living bacteria tested both for safety and potency. Current vaccines have not been demonstrated to be effective. Efficacy is only inferred from prior experiments and experience with older vaccines both here and abroad.

Schedules for Immunization.—BCG immunization should be seriously considered for the following groups: (1) infants who are skin-test-negative, but who are repeatedly exposed in a household to individuals with pulmonary tuberculosis; (2) individuals and groups in whom tuberculosis is prevalent and for whom health measures to contain or control the disease are not readily available; and (3) tuberculin-negative health workers who are at increased risk of repeated exposure.[58,59]

Since children with a positive tuberculin skin test should not receive BCG, prior tuberculin testing must be done. In infants younger than 2 months of age, prior tuberculin testing is unnecessary, particularly if the infant has not been exposed to tuberculosis. In some vaccine campaigns, such as those conducted by the World Health Organization, prior tuberculin testing has not been done.

BCG should not be given to individuals who may have immunodeficiencies or are receiving immunosuppressant drugs or who have skin infections or thermal burns. BCG has been used for malnourished subjects and for newborns, including prematures. These conditions do not seem to be a contraindication if the tuberculosis risk is high although cell-mediated immunity is depressed and BCG dissemination is a possibility.

BCG is usually administered intradermally over the deltoid or triceps muscle. Newborn infants each receive .05 mL, and older infants, children, and adolescents receive 0.1 mL. A multiple-puncture procedure is an alternative method. Further information and equipment are obtainable from the same sources that supply the vaccine, which are indicated in the footnote at the end of the article.

Side Effects and Adverse Reactions.—The most common side effect of BCG is regional lymphadenitis.[60] This complication is important to recognize since the lymph nodes involved may become large, often simulating lymphoma or other more serious lymph node diseases. Rarely, prolonged ulceration at the vaccination site occurs.

Even more rarely, disseminated BCG infection and death can occur among immunodeficient individuals. Osteomyelitis and lupus-like disease have occasionally been observed.

Tularemia

Infection with *Francisella tularensis* causes tularemia. The organism is found in infected wild and domestic animals and in the ticks, flies, and other insects that bite them. Inoculation occurs via skin or conjunctiva directly or by the bites of infected insects. It may also occur via ingestion of contaminated water or of an infected and inadequately cooked animal or via inhalation.[61,62] Infection occurs readily among laboratory personnel working with the organism.[63]

Francisella tularensis is a facultative intracellular parasite; in animals, immunity depends largely on cellular, rather than humoral, mechanisms.[64,65] Even documented infection with virulent organisms does not prevent reinfection.

Immunization is only recommended for persons at high risk of infection, ie, laboratory workers; children almost never require tularemia immunization. The vaccine consists of live attenuated bacteria produced from a colony-type variant of *F tularensis*. Immunization does not prevent entirely, but does reduce substantially, the incidence of typhoidal tularemia.[63] The occurrence of ulceroglandular tularemia remains the same, but the severity of this disease is decreased.

One drop of vaccine is inoculated by multiple punctures. Local inflammation occurs, and healing with scarring and occasional enlargement of regional lymph nodes ensues, but no systemic reaction is encountered. Inoculation of contacts of cases is unnecessary.

THE FUTURE OF IMMUNIZATION AGAINST BACTERIAL DISEASES

Currently used bacterial vaccines are disappointing when viewed in contrast with viral immunization. The future of bacterial vaccines depends on better understanding of natural immunity, exploration of new vaccines, and improved technology. Some exciting trends can be gleaned in current investigative efforts.

Mimicry of the natural *route* of infection offers theoretical immunologic advantage for some bacterial immunization. Local or topical immune mechanisms might be stimulated by living or killed bacteria placed on the respiratory mucosa or ingested, exposing the GI tract. Experience with live polio vaccines and inactivated influenza vaccines suggest that topical antibody production can be stimulated. An experimental attempt at duplicating this phenomenon for bacteria is the intranasal inoculation of purified type-specific group A streptococcal M-protein vaccines that reduces both colonization and clinical illness after challenge with homologous organisms. Oral administration of live, attenuated shigellae has been shown to be effective in reducing the frequency and severity of type-specific disease in endemic settings.

Current cholera vaccines, both bacterial somatic and toxoid, are disappointing in both the degree and duration of immunity produced. Experimental evidence suggests that local antibody is an important component in human immunity. Studies are under way to develop and evaluate the effectiveness of orally administered live and killed cholera vaccines.

Another new idea occurred as the result of the discovery of cross-reacting antigens in seemingly unrelated organisms. For example, certain types of *Escherichia coli* share antigens with *Haemophilus* sp and with meningococci. Asymptomatic infection with the K-100 type of *E coli* stimulates antibody against *H influenzae*, type B. Similarly, K-1 strains of *E coli* induce antibody cross-reaction with the group B meningococcus. Although far from practical use, this line of investigation opens up the possibility of protection by use of an innocuous organism, possibly overcoming the difficulties experienced in current attempts at protection against these imported pediatric diseases.

Development of improved vaccines continues for pertussis, *H influenzae*, and the meningococci, particularly group B. The goal is vaccines for each that are safe and antigenic for the extremely young infant, for whom the risk of disease with these organisms is high.

Attempts to dissect the pertussis organism into antigenic units, which avoid the side effects of current whole bacteria vaccines, are in progress. A protein derivative from the outer membranes of group B meningococcus is being evaluated for adults. A new protein-polysaccharide complex from *H influenzae* has been tested in adults and is available for study in older children. These and other approaches offer the possibility of new and improved bacterial vaccines for pediatric practice in the future.

The vaccine for anthrax is available from the Center for Disease Control, Atlanta, on request. Current BCG vaccine can be obtained from ITR Biomedical Research, University of Illinois Medical Center, 904 W Adams St, Chicago, IL 60607; and Glaxo Laboratories, Ltd, Greenford, Middlesex, England (distributed in the United States by Eli Lilly Co). The vaccine is delivered in a freeze-dried state and should be reconstituted, protected from exposure to light, and used within eight hours of reconstitution.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*
Rifampin—*Rifadin, Rimactane.*

References

1. Parish HJ: *Victory With Vaccines.* Edinburgh, E & S Livingstone, 1968.
2. Parish HJ: *A History of Immunization.* Edinburgh, E & S Livingstone, 1965.
3. Mudd S: *Infectious Agents and Host Reactions.* Philadelphia, WB Saunders Co, 1970.
4. Bellanti J: Mechanisms of immunity to bacterial diseases, in Bellanti J (ed): *Immunology, II.* Philadelphia, WB Saunders Co, 1978.
5. Brooks GF, Bennett JV, Feldman RA: Diphtheria in the United States: 1959-1970. *J Infect Dis* 129:172-178, 1974.
6. Munford RS, Ory HW, Brooks GF, et al: Diphtheria deaths in the United States, 1959-1970. *JAMA* 229:1890-1893, 1974.
7. Nelson LA, Peri BA, Rieger CHL, et al: Immunity to diphtheria in an urban population. *Pediatrics* 61:703-710, 1978.
8. World Health Organization: Diphtheria and pertussis vaccination: I. Diphtheria. *WHO Tech Rep Ser* 61:8-21, 1963.
9. Volk VK, Gottshall RY, Anderson HD, et al: Antigenic response to booster dose of diphtheria and tetanus toxoids. *Pub Health Rep* 77:185-194, 1962.
10. *Report of the Committee on Infectious Diseases,* ed 18. Evanston, IL, American Academy of Pediatrics, 1977.
11. Miller LW, Bickham S, Jones W, et al:

Diphtheria carriers and the effect of erythromycin therapy. *Antimicrob Agents Chemother* 6:166-169, 1974.

12. Barkin RM, Pichichero ME: Diphtheria-pertussis-tetanus vaccine: Reactogenicity of commercial products. *Pediatrics* 63:256-260, 1979.

13. Weinstein L: Tetanus. *N Engl J Med* 289:1293-1296, 1973.

14. Rothstein RJ, Baker FJ: Tetanus: Prevention and treatment. *JAMA* 240:675-676, 1978.

15. Brooks VB, Curtis DR, Eccles JC: Mode of action of tetanus toxin. *Nature* 175:120-121, 1955.

16. Turner TB, Velasco-Joven EA, Prudovsky S: Studies on the prophylaxis and treatment of tetanus: I. Studies pertaining to treatment. *Bull Johns Hopkins Hos* 102:71-84, 1958.

17. Steigman AJ: Abuse of tetanus toxoid. *J Pediatr* 72:753-754, 1968.

18. Fulthorpe AJ: The influence of mineral carriers on the simultaneous active and passive immunization of guinea-pigs against tetanus. *J Hyg* 63:243-262, 1965.

19. Scheibel I, Bentzon MW, Christensen PE, et al: Duration of immunity to diphtheria and tetanus after active immunization. *Acta Pathol Microbiol Scand* 67:380-392, 1966.

20. Edsall G: The current state of tetanus immunization. *Hosp Pract* 6:57-66, 1971.

21. Aftandelians R, Connor JD: Immunologic studies of pertussis. *J Pediatr* 83:206-214, 1973.

22. Whooping-cough immunisation, leading article. *Br Med J* 2:5-6, 1977.

23. Grady GF, Wetterlow LH: Pertussis vaccine: Reasonable doubt? *N Engl J Med* 298:966-967, 1978.

24. Baraff LJ, Wilkins J, Wehrle PF: The role of antibiotics, immunization and adenoviruses in pertussis. *Pediatrics* 61:224-230, 1978.

25. Griffith AH: Reactions after pertussis vaccine: A manufacturer's experiences and difficulties since 1964. *Br Med J* 1:809-815, 1978.

26. Stewart GT: Vaccination against whooping cough: Efficacy versus risks. *Lancet* 1:234-239, 1977.

27. Katz SL, Wilfert CM: New thoughts on pertussis. *Pediatrics* 63:841-842, 1979.

28. Strom J: Is universal vaccination against pertussis always justified? *Lancet* 2:1184-1186, 1960.

29. MacLeod CM, Hodges RG, Heidelberger M, et al: Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J Exp Med* 82:445-465, 1945.

30. Austrian R: Random gleanings from a life with a pneumococcus. *J Infect Dis* 131:474-484, 1975.

31. Austrian R: Pneumococcal infection and pneumococcal vaccine. *N Engl J Med* 297:938-939, 1977.

32. Cowan MJ, Ammann AJ, Wara DW, et al: Pneumococcal polysaccharide immunization in infants and children. *Pediatrics* 62:721-727, 1978.

33. Ammann AJ, Addiego J, Wara DW, et al: Polyvalent pneumococcal polysaccharide immunization of patients with sickle-cell anemia and patients with splenectomy. *N Engl J Med* 297:897-900, 1977.

34. Sullivan JL, Ochs HD, Schiffman G, et al: Immune response after splenectomy. *Lancet* 1:178-182, 1978.

35. Fikrig SM, Schiffman G, Phillipp JC, et al: Antibody response to capsular polysaccharide vaccine of *Streptococcus pneumoniae* in patients with nephrotic syndrome. *J Infect Dis* 137:818-821, 1978.

36. Cadman E, Cohen MS, Root RK, et al: Impaired response to pneumococcal vaccine in Hodgkin's disease. *N Engl J Med* 299:1317-1318, 1978.

37. Goldschneider I, Gotschlich EC, Artenstein MS: Human immunity to the meningococcus: I. The role of humoral antibodies. *J Exp Med* 129:1307-1326, 1969.

38. Goldschneider I, Gotschlich EC, Artenstein MS: Human immunity to the meningococcus: II. Development of natural immunity. *J Exp Med* 129:1327-1348, 1969.

39. Brandt BL, Smith CD, Artenstein MS: Immunogenicity of serogroup A and C *Neisseria meningitidis* polysaccharide vaccines administered together in humans. *J Infect Dis* 137:202-205, 1978.

40. Peltola H, Mäkelä PH, Käyhty H, et al: Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children 3 months to 5 years of age. *N Engl J Med* 297:686-691, 1977.

41. Peltola H, Käyhty H, Kuronen T, et al: Meningococcus group A vaccine in children 3 months to 5 years of age. *J Pediatr* 92:818-822, 1978.

42. Wyle FA, Artenstein MS, Brandt BL, et al: Immunologic response of man to group B meningococcal polysaccharide vaccine. *J Infect Dis* 126:514-521, 1972.

43. Zolliger WD, Mandrell RE, Altieri P, et al: Safety and immunogenicity of a *Neisseria meningitidis* type 2 protein vaccine in animals and humans. *J Infect Dis* 137:728-739, 1978.

44. Advisory committee on immunization practices: Meningococcal polysaccharide vaccines. *Morbidity Mortality Weekly Rep* 27:327-329, 1978.

45. Wilkins J, Wehrle PF: Further characterization of responses of infants and children to meningococcal A polysaccharide vaccine. *J Pediatr* 94:828-832, 1979.

46. Who should be given meningococcal vaccine? Editorial. *Lancet* 2:1185-1186, 1978.

47. Center for Disease Control: Cholera vaccine. *Morbidity Mortality Weekly Rep* 27:173-174, 1978.

48. Center for Disease Control: Plague vaccine. *Morbidity Mortality Weekly Rep* 26:393, 1977.

49. Center for Disease Control: Typhoid vaccine. *Morbidity Mortality Weekly Rep* 27:231-233, 1978.

50. Benenson AS (ed): *Control of Communicable Diseases in Man*, ed 12. Washington, DC, American Public Health Association, 1975, pp 12-15.

51. Van Ness GB: Ecology of anthrax. *Science* 172:1305-1307, 1971.

52. Anthrax in humans, United States 1978. *Morbidity Mortality Weekly Rep* 28:160-165, 1979.

53. Wright GG, Green TW, Kanode RG Jr: Studies on immunity in anthrax: Immunizing activity of alum-precipitated protective antigen. *J Immunol* 73:387-391, 1954.

54. Brachman PS, Gold H, Plotkin SA, et al: Field evaluation of human anthrax vaccine. *Am J Public Health* 52:632-645, 1962.

55. American Thoracic Society: BCG vaccines for tuberculosis. *Am Rev Respir Dis* 112:478-480, 1975.

56. Stilwell JA: Benefits and costs of the schools BCG vaccination programme. *Br Med J* 1:1002-1004, 1976.

57. Comstock GW, Livesay VT, Woolpert SF: Evaluation of BCG vaccination among Puerto Rican children. *Am J Public Health* 64:283-291, 1974.

58. Center for Disease Control: BCG vaccination. *Morbidity Mortality Weekly Rep* 28:241-244, 1979.

59. Heyworth B, Mullinger BM: Neonatal vaccination with "universal strength" BCG vaccine. *Arch Dis Child* 52:503-504, 1977.

60. Chaves-Carballo E, Sanchez GA: Regional lymphadenitis following BCG vaccination (BCGitis). *Clin Pediatr* 11:693-697, 1972.

61. Sullivan JL, Ochs HD, Schiffman G, et al: Immune response after splenectomy. *Lancet* 1:178-182, 1978.

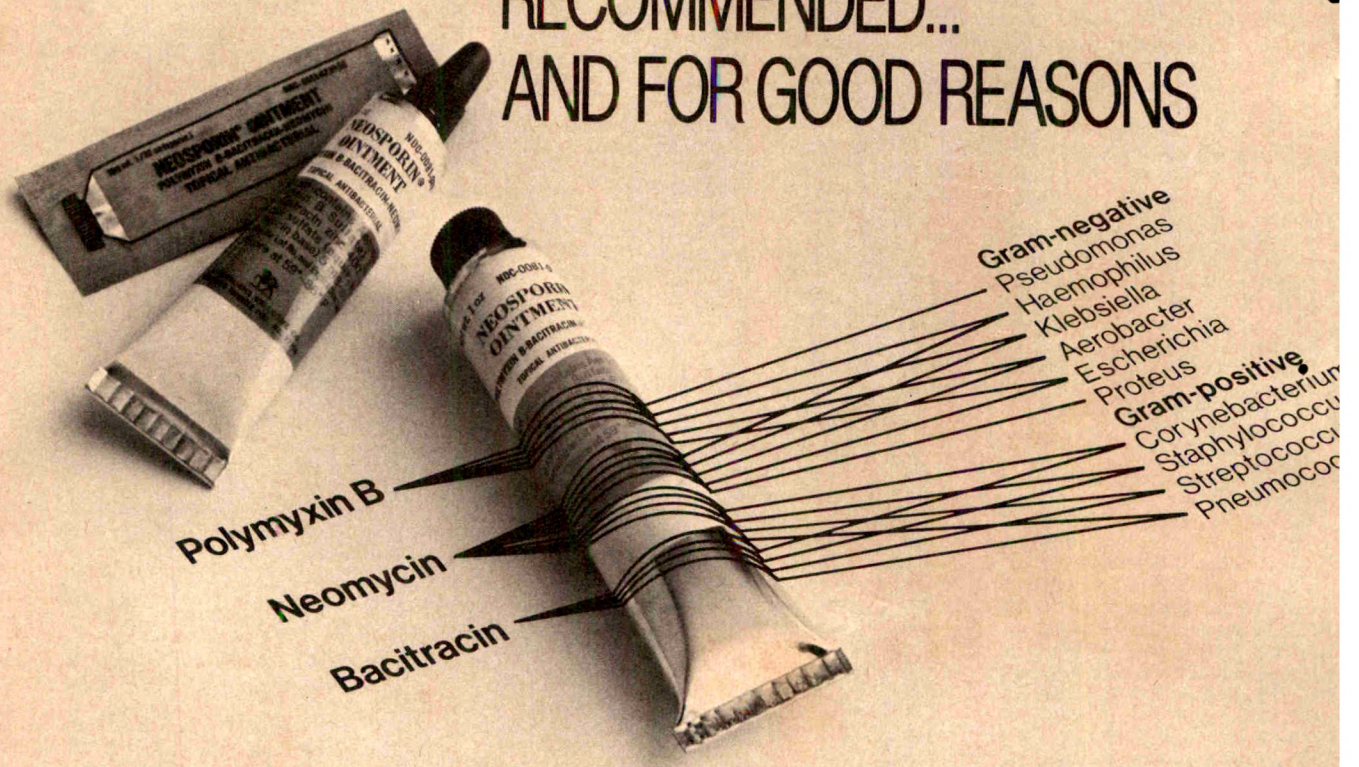
62. Guerrant RL, Humphries MK Jr, Butler JE, et al: Tickborne oculoglandular tularemia. *Arch Int Med* 136:811-813, 1976.

63. Burke DS: Immunization against tularemia: Analysis of the effectiveness of live *Francisella tularensis* vaccine in prevention of laboratory-acquired tularemia. *J Infect Dis* 136:55-60, 1977.

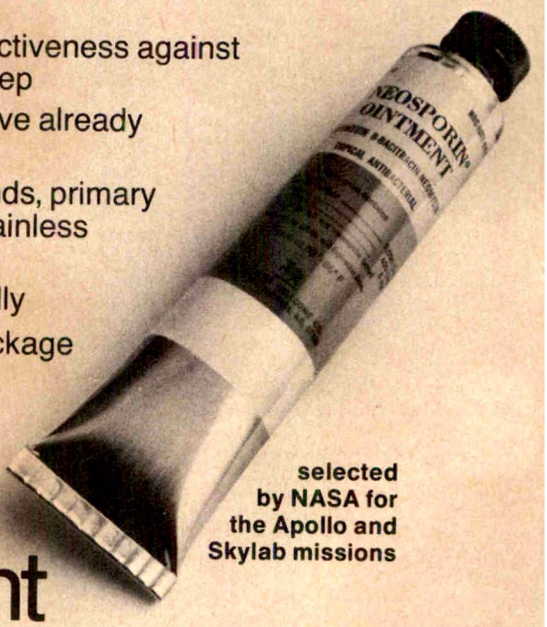
64. Claflin JL, Larson CL: Infection-immunity in tularemia: Specificity of cellular immunity. *Infect Immun* 5:311-318, 1972.

65. Kostiala AAI, McGregor DD, Logie PS, et al: Tularemia in the rat: I. The cellular basis of host resistance to infection. *Immunology* 28:855-869, 1975.

IT'S HIGHLY RECOMMENDED... AND FOR GOOD REASONS



1. provides broad-spectrum, overlapping antibacterial effectiveness against common susceptible pathogens, including staph and strep
2. helps prevent topical infections, and treats those that have already started
3. it's good medicine for abrasions, lacerations, open wounds, primary pyodermas, secondarily infected dermatoses; and it's painless and cosmetically pleasing
4. contains three antibiotics that are rarely used systemically
5. you can recommend it in any of the three convenient package sizes: 1 oz tube, ½ oz tube, or the versatile, single-use foil packet



selected by NASA for the Apollo and Skylab missions

NEOSPORIN® Ointment

(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

ONE HUNDRED YEARS WELLCOME

Burroughs Wellcome Co.
Research Triangle Park
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Radiological Case of the Month

Lionel W. Young, MD;

Contributed by James W. Lowell, MD, Bertram R. Girdany, MD

This 5-year-old girl was referred to an orthopedic surgeon because of pain in her left wrist for a period of weeks. Three months previously, she had hurt the dorsum of her left hand and wrist in a fall. The lateral aspect of the dorsum of the hand was swollen. A roentgenogram of the left hand was obtained (Fig 1 and 2). A chest roentgenogram was normal. Skin tests for microbacterial and fungal causes were negative. A complete blood cell count was normal. The carpal lesion underwent biopsy and was partially resected.

From the Department of Radiology (Dr Lowell), St Joseph Mercy Hospital, Pontiac, Mich; and the Department of Radiology (Dr Girdany), Children's Hospital of Pittsburgh.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).

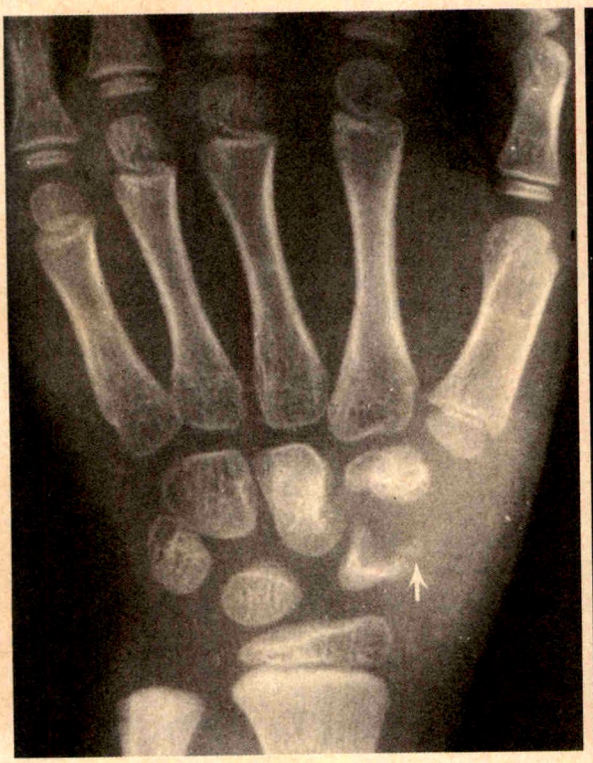


Figure 1.

Figure 2.

Denouement and Discussion

Fig 1.—Anteroposterior view of left wrist. There is erosive bone destruction of most of navicula, lateral margin of capitate, and proximal margin of lesser multiangular area. Note calcification (arrow) adjacent to navicula and surrounding soft-tissue swelling.

Fig 2.—Lateral view of left wrist. Note erosion of lesser multiangular area (arrowhead) and soft-tissue swelling.

Fig 3.—Microscopic section in low-power magnification (hematoxylin-eosin, ×90). See first paragraph of "Discussion."

Fig 4.—Microscopic section in high-power magnification (hematoxylin-eosin, ×500). See first paragraph of "Discussion."

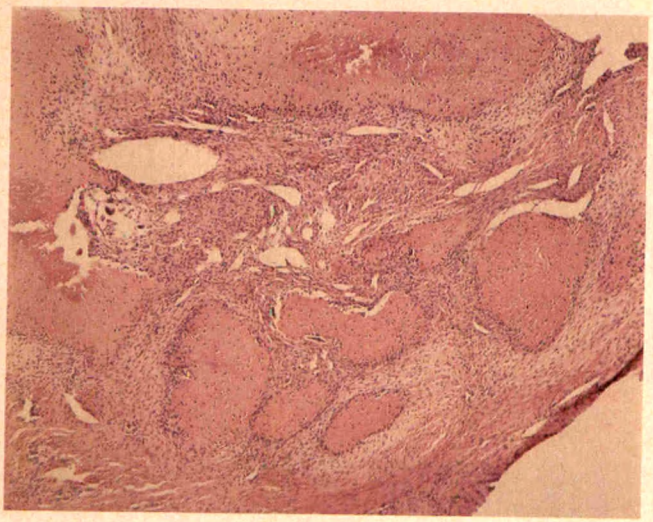


Figure 3.

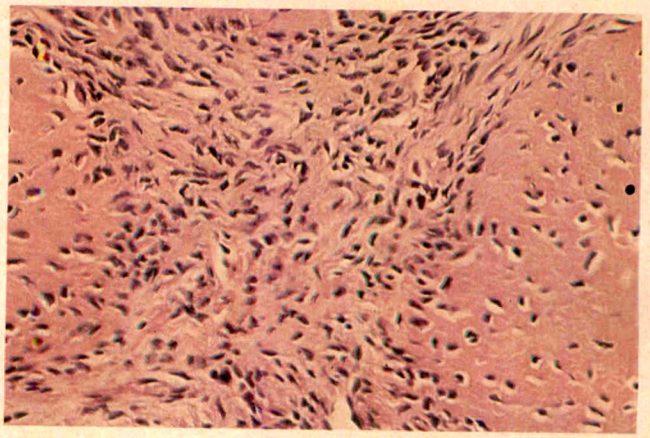


Figure 4.

Juvenile Aponeurotic Fibroma

Microscopic examination of sections of the lesion (Fig 3 and 4) showed degenerating focally hyalinized fibrocartilagenous tissue and fragments of proliferating fibroblastic cells arranged in nodules, palisading or intertwining tangles of eosinophilic spindle-shaped cells. Nuclei were oval or spindle shaped, moderately hyperchromatic, and uniform in size. Several islands of cartilagenous metaplasia with focal calcification were present within an area of neoplastic cell proliferation, but there was no evidence of malignancy. The findings were diagnostic of juvenile aponeurotic fibroma (JAF).

Juvenile aponeurotic fibroma is a rare, benign neoplasm of the fascia, aponeuroses, and muscles, usually of the hands and wrists or feet and ankles of children and adolescents.[1-3] It is more common in boys, but does not follow a definite history of trauma. The mass may be circumscribed or diffuse and is usually painless.[4] Although JAF is infiltrative and infrequently recurrent, malignant degeneration has not been reported.[5] The lesion may be grouped with other relatively nonaggressive fibromatoses among which are congenital generalized fibromatosis, fibromatosis colli, fibrous hamartoma of infancy, recurring digital fibrous tumor of Reye, juvenile hyaline fibromatosis, diffuse infantile fibromatosis, and hereditary gingival fibromatosis.[6]

Roentgenographically, JAF appears as a soft-tissue mass that may be stippled with calcium and that erodes adjacent bone (Fig 1 and 2). The differential diagnosis includes giant-cell tumor of the tendon sheath, fibrous lymphoma of the tendon sheath, soft-tissue chondroma, periosteal chondroma, and synovial sarcoma.[6]

This neoplasm is composed of dense cellular fibrous tissue that infiltrates fat, muscles, collagen bundles, nerves, and adjacent bones, and it is unencapsulated.[4,7-9] It may be distinguished from other fibromatoses by focal chondroid differentiation within a proliferation of spindle cells. Palisading calcifications occur within the lesion.

In spite of frequent recurrences, management of JAF has been conservative because of the unlikelihood of malignant degeneration. In follow-up of this girl during a three-year period, she has had no pain, tenderness, or swelling of the wrist after partial resection of the lesion.

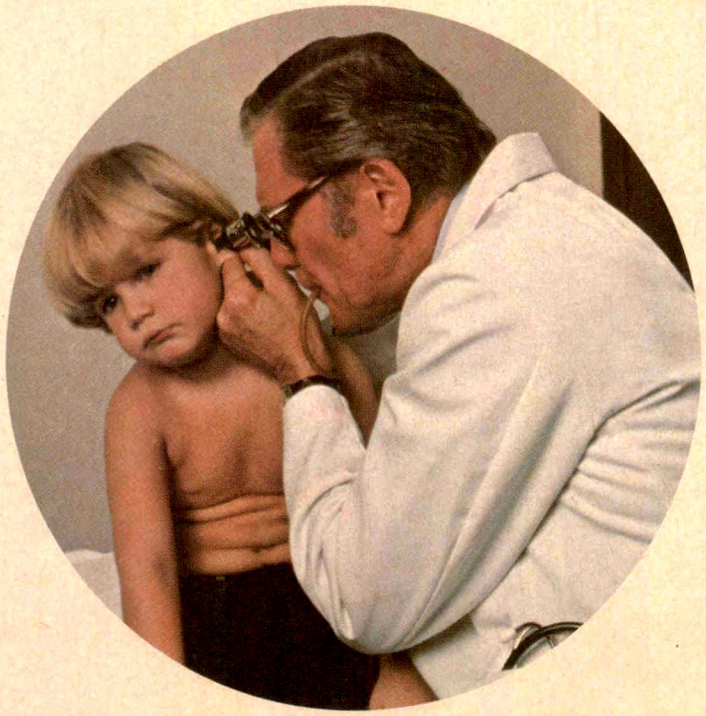
References

1. Cavanagh RC: Tumors of the soft tissues of the extremities. *Semin Roentgenol* 8:73-89, 1973.
2. Keasbey LE: Juvenile aponeurotic fibroma (calcifying fibroma): Distinctive tumor arising in the palms and soles of young children. *Cancer* 6:338-346, 1953.
3. Keasbey LE, Fansleau HA: The aponeurotic fibroma. *Clin Orthop* 19:115-131, 1961.
4. Allen PW, Enzinger FM: Juvenile aponeurotic fibroma. *Cancer* 26:857-867, 1970.
5. Keller RB, Baez-Giangreco A: Juvenile aponeurotic fibroma. *Clin Orthop* 106:198-205, 1975.
6. Karasick D, O'Hara AE: Juvenile aponeurotic fibroma. *Radiology* 123:725-726, 1977.
7. Goldman RL: The cartilage analogue of fibromatosis (aponeurotic fibroma). *Cancer* 26:1325-1331, 1970.
8. Lichtenstein L, Goldman RL: The cartilage analogue of fibromatosis: A reinterpretation of the condition called "juvenile aponeurotic fibroma." *Cancer* 17:810-816, 1964.
9. Stout AP, Lattes R: Benign tumors and tumor-like proliferations, in Firminger HI (ed): *Tumors of the Soft Tissues.* Atlas of Tumor Pathology, Armed Forces Institute of Pathology, 1967, series 2, pp 22-23.

From
Lilly
Research

Ceclor®
cefaclor

A newly developed oral antibiotic useful in acute otitis media*



A newly developed oral antibiotic

Ceclor® cefaclor

Consider the changing bacterial

Increasing incidence of otitis media caused by H. influenzae

Reports from many areas of the country show that the bacterial pattern seen in otitis media is changing. Published studies suggest that the incidence of otitis media caused by *H. influenzae* is increasing.[1,2]

In fact, the American Academy of Pediatrics' Committee on Infectious Diseases reports that relapses of otitis media have been more common with *H. influenzae* than with other organisms.[3]

H. influenzae resistance is a growing problem

Percentage of Ampicillin-Resistant *H. influenzae* Isolates*

	1975	1976	1977
Boston[4]	5.3%	10.2%	15.6%
Fresno[5]	—	—	4.8
Huntsville[4]	1.4	2.8	13.6
Washington, D.C.[6]	1.6	18	35
Oklahoma City[7]	—	—	22

*Isolates obtained from a variety of body fluids (middle-ear exudate, blood, etc.).

Recommendations regarding treatment of otitis media caused by H. influenzae

The American Academy of Pediatrics, in its recommendations for the treatment of otitis media, reports that *H. influenzae* is often the suspected pathogen in children less than eight years of age. They further report that ampicillin-resistant strains of *H. influenzae* have been isolated. The physician should therefore consider ampicillin resistance in the child with acute otitis media, particularly one who does not show clinical improvement after 48 to 72 hours of ampicillin therapy.[8]

Investigators have suggested a need for alternative antimicrobials in the treatment of otitis media caused by ampicillin-resistant *H. influenzae*.[9,10]

Ceclor® (cefaclor) is effective in the treatment of acute otitis media due to susceptible strains of these microorganisms:

- *S. pneumoniae*
- *H. influenzae* (including beta-lactamase-producing ampicillin-resistant strains)
- Staphylococci (including coagulase-positive, coagulase-negative, and penicillinase-producing strains)
- *S. pyogenes* (group A beta-hemolytic streptococci)

In studies of 246 patients with otitis media, Ceclor demonstrated a 93 percent clinical and bacteriologic success rate (see accompanying chart).[11]

Clinical and Bacteriologic Responses by Pathogen in 246 Infants and Children with Otitis Media[11]

		Satisfactory Responses	
Pathogen	Number of Patients	Clinical (Symptomatic)	Bacteriologic
S. pneumoniae	127	121	121
S. pyogenes	11	11	11
Staphylococcus aureus	21	18	19
H. influenzae	74	67	66
Multiple organisms	13	12	12
Totals	246	229 (93%)	229 (93%)

See the following page for criteria for diagnosis and response.

pattern of acute otitis media*

Good taste and t i d administration may aid patient compliance

Ceclor may be administered t i d. The pleasant-tasting oral suspensions encourage patient cooperation:

125 mg/5 ml, strawberry flavor
250 mg/5 ml, grape flavor

Criteria for diagnosis and response

Diagnosis:
Diagnosis of otitis media was confirmed in all patients by culture of middle-ear aspirate or exudate within 24 hours after the start of therapy. Exudate was acceptable as a culture source for only pneumococci, *H. influenzae*, and group A streptococci. Additional specimens for culture were obtained during and after therapy as deemed necessary by the clinician. The bacteriologic response was based on results during the ten to 16-day posttherapy follow-up period.

Clinical (symptomatic) response:
Satisfactory = disappearance of or improvement in signs and symptoms of the principal infection, with or without recurrence of signs or symptoms during the posttherapy follow-up period.

Unsatisfactory = no improvement in signs and symptoms at the end of therapy.

Bacteriologic response:
Cure = pathogen(s) eliminated or reduced to insignificant numbers during therapy or elimination of the original pathogen during therapy, followed by a culture positive for a new pathogen (reinfection) either during therapy or during the posttherapy follow-up period.

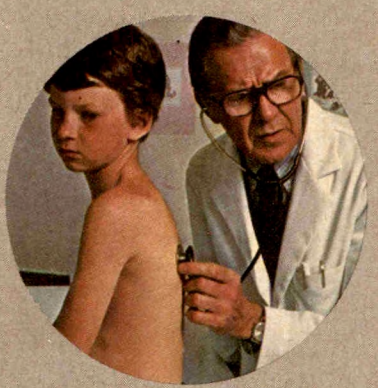
Failure = failure of the treatment to eradicate the pathogen(s) or initial eradication of the pathogen(s), followed by relapse with the same pathogen during therapy or during the posttherapy follow-up period.

Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

*Due to susceptible strains of *S. pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes*.

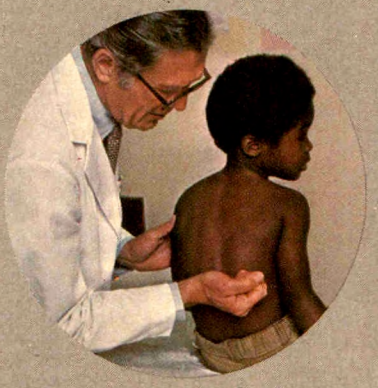
Ceclor® (cefaclor) is also indicated for these other common infections

Clinical trials have demonstrated the effectiveness of Ceclor against the following common infections when caused by susceptible strains of the designated microorganisms:



Lower respiratory infections
including pneumonia caused by *S. pneumoniae*, *H. influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Upper respiratory infections
including pharyngitis and tonsillitis caused by *S. pyogenes* (group A beta-hemolytic streptococci)



Urinary tract infections
including pyelonephritis and cystitis caused by *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and coagulase-negative staphylococci

Skin and skin-structure infections
caused by *S. aureus* and *S. pyogenes* (group A beta-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See summary of prescribing information.

See the following page for summary of prescribing information.

000099

A newly developed oral antibiotic

Ceclor® cefaclor

Pediatric Dosage			
Mild to Moderate Infections (20 mg/kg/day)			
125 mg (½ tsp t i d)	**125 mg** (1 tsp t i d)	**250 mg** (1 tsp t i d)	
0-20 lb 0-9 kg	20-40 lb 9-18 kg	40-55 lb 18-25 kg	
More Serious Infections and Otitis Media* (40 mg/kg/day)			
125 mg (½ tsp t i d)	**125 mg** (1 tsp t i d)	**250 mg** (1 tsp t i d)	**250 mg** (1 gm in 3 divided doses)
0-10 lb 0-4.5 kg	10-20 lb 4.5-9 kg	20-40 lb 9-18 kg	40-55 lb 18-25 kg

125 mg, Strawberry 250 mg, Grape

The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every eight hours.

In more serious infections, otitis media,* and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 gm per day.

Safety for use in infants less than one month of age has not been established.

*Due to susceptible strains of *S. pneumoniae, H. influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).

References

1. Pediatr. Clin. North Am., *21*:379, 1974.
2. J.A.M.A., *238*:1032, 1977.
3. Report of the Committee on Infectious Diseases, p. 109. Evanston, Illinois: American Academy of Pediatrics, 1977.
4. J. Pediatr., *92*:889, 1978.
5. West. J. Med., *128*:101, 1978.
6. J.A.M.A., *239*:320, 1978.
7. Med. Trib., *18*:1 (November 16), 1977.
8. Report of the Committee on Infectious Diseases, p. 162. Evanston, Illinois: American Academy of Pediatrics, 1977.
9. Curr. Chemother., *1*:123, 1978.
10. Am. J. Dis. Child., *132*:992, 1978.
11. Data on file, Eli Lilly and Company.

Ceclor® (cefaclor)

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci)

Lower respiratory infections, including pneumonia caused by *S. pneumoniae (D. pneumoniae), H. influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Upper respiratory infections, including pharyngitis and tonsillitis caused by *S. pyogenes* (group A beta-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections, including pyelonephritis and cystitis caused by *Escherichia coli, Proteus mirabilis, Klebsiella* species, and coagulase-negative staphylococci

Skin and skin-structure infections caused by *Staphylococcus aureus* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor® (cefaclor, Lilly), should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below:

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

Administration and Dosage:

Ceclor® (cefaclor, Lilly) is administered orally.

Adults—The usual adult dosage is 250 mg every eight hours. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled. Doses of 4 gm per day have been administered safely to normal subjects for 28 days, but the total daily dosage should not exceed this amount.

Children—The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every eight hours, as indicated:

Child's Weight	Ceclor Suspension 125 mg/5 ml	Ceclor Suspension 250 mg/5 ml
9 kg	1/2 tsp t i d	
18 kg	1 tsp t i d	1/2 tsp t i d

In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 gm per day.

Ceclor may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see Precautions).

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of Ceclor should be administered for at least ten days. [070379]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46206.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

Lilly

000099

Spontaneous Splenic Rupture in Acute Lymphoblastic Leukemia: Successful Nonoperative Management

Spontaneous rupture of the spleen is a rare complication in patients with acute leukemia.[1-8] In most of the patients diagnosis has been made postmortem, though successful removal of the spleen has been accomplished in a few. Recently, we encountered a case of acute T-cell leukemia in which intraperitoneal bleeding and shock were due to splenic rupture. The patient's condition was managed successfully without surgical intervention.

Report of a Case.—A 13-year-old boy was admitted to Children's Hospital of Michigan, Detroit, on June 14, 1978, with a two-week history of mild difficulty in breathing, generalized petechiae, prominent bilateral cervical adenopathy, and hepatomegaly (5 cm) and splenomegaly (7 cm). The following laboratory values were reported: hemoglobin, 14.2 g/dL; WBCs, 174,000/cu mm, with 90% lymphoblasts; and platelets, 28,000/cu mm. Chest roentgenogram showed an enlarged thymus. Bone marrow examination confirmed the diagnosis of acute lymphoblastic leukemia, and the leukemic blasts formed spontaneous rosettes with sheep erythrocytes, indicating the T-cell nature of the blast cells. The uric acid value was 24 mg/dL, and the BUN level was 24 mg/dL.

Initial treatment was aimed at prevention of serious bleeding complications and uric acid nephropathy. Pooled platelet transfusion (10 units) was given on the day of admission and again the next evening. A single course of radiotherapy (50 rads) was given to the neck and upper part of the chest on the second hospital day to relieve the respiratory difficulty. Vigorous alkalinization of the urine and allopurinol administration resulted in a reduction of the uric acid level to 9.6 mg/dL and the BUN value to 11.5 mg/dL on the fifth hospital day. Other laboratory values were as follow: hemoglobin, 10.7 g/dL; hematocrit, 34%; WBCs, 93,000/cu mm; and platelets, 9,000/cu mm. Arrangements for platelet transfusions were made and start of chemotherapy planned.

However, he suddenly complained of severe pain in the left shoulder and left side of the chest and became restless. Physical examination showed no abnormalities. The pain and restlessness subsided spontaneously within a few minutes, but the patient felt weak. Approximately two hours later, he was found to be extremely pale, incoherent, and in shock. Pulse rate was 126 beats per minute; blood pressure (BP) 90/70 mm Hg; and respiratory rate, 34/min. The abdomen was soft and there was tenderness in the left upper quadrant. The previously enlarged spleen was now difficult to palpate. Bowel sounds were normal.

There was no history of trauma and no obvious evidence of blood loss such as hematemesis, melena, or rectal bleeding. The patient was immediately given 1,050 mL of packed RBCs (PRBCs) and 10 units of pooled platelets, along with normal saline solution and hydrocortisone sodium succinate, 150 mg every six hours. With these measures, the BP rapidly increased to 120/60 mm Hg, and the patient became oriented and alert.

The abdomen, however, was noted to be distended, with tenderness in the epigastrium and shifting dullness. In spite of the large volume of blood transfused, the hemoglobin level was 9.9 g/dL. A possible splenic rupture was suspected, and a plain film of the abdomen showed intraperitoneal fluid.

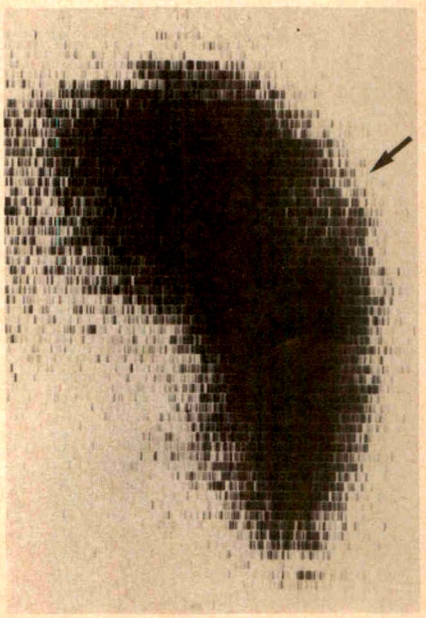
During the next 24 hours, transfusion of 2,000 mL of whole blood and platelet transfusions 12 hours apart were necessary to maintain a hemoglobin level of more than 10 g/dL and normal BP. Subsequently, platelet transfusions were given twice daily. This apparently controlled the bleeding as he required the transfusion of PRBCs only once more.

Hydrocortisone administration was continued and remission induction was begun with vincristine sulfate therapy on the seventh hospital day. This was followed by a rapid increase in the BUN level to 134 mg/dL, necessitating hemodialysis daily for five days. By the 15th hospital day, the patient's overall condition stabilized, the platelet counts began to increase, and the platelet transfusions were discontinued. Sodium pertechnetate Tc 99m spleen scan performed two weeks after the episode of shock showed a cold spot in the left upper pole, thus confirming a splenic hematoma or rupture (Figure).

The patient subsequently completed the initial induction chemotherapy and was in hematologic remission by Aug 4, 1978. Initial remission lasted six months, and the patient died in refractory relapse on July 2, 1979.

Comment.—Considering the vascularity of the spleen, its lack of supportive tissue, and the thin splenic capsule, it is surprising to find that spontaneous rupture of the spleen is a rare occurrence in acute leukemia. Thus far, only 19 cases of spontaneous splenic rupture in acute leukemia have been reported.[1,3,5-8] The acute leukemia was of the lymphoid type in nine, and only one patient was in the pediatric age group.[3]

In our patient, the intraperitoneal bleeding most likely occurred from a subcapsular infarction of the spleen, with subsequent tear through the capsule. The infarction probably occurred



Sodium pertechnetate Tc 99m scan of spleen showing area of decreased uptake (arrow) in upper part of spleen.

at the time the patient experienced severe left shoulder and left lower chest pain. Such symptoms occurred in almost all of the previously reported cases, with the onset of shock delayed, as in our patient, by a few hours to several days. Our experience suggests that, rare as it may be, splenic infarction should be suspected in any leukemic patient with similar findings and that such patients should be monitored closely for signs of impending shock. A splenic scan may be a valuable aid in the final diagnosis.

Splenectomy for rupture of the spleen has been the standard mode of therapy until now. In recent years, owing to the realization of susceptibility to overwhelming infection in splenectomized individuals, splenorrhaphy and nonoperative management of splenic rupture are becoming more common.[9-11] Howman-Giles et al[10] recommended nonoperative management in selected children with traumatic rupture of the spleen who are clinically stable or can be maintained in a stable condition with intravenous fluids or blood.

The management of splenic rupture in a leukemic patient in relapse poses special problems because of the thrombocytopenia and susceptibility to infections. In our case, vigorous treatment with repeated platelet transfusions and PRBC transfusions stabilized his condition and controlled the bleeding, and the subsequent complete recovery negated the need for splenectomy.

In retrospect, this case illustrates that nonoperative management of splenic rupture can be successful even in thrombocytopenic patients. This method of treatment should be considered in all patients with splenic rupture unless the patient's condition cannot be stabilized. To our knowledge, this is the first reported example of successful nonoperative management of spontaneous rupture of the spleen in a leukemic patient.

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Bryce Alpern, MD, referred this patient. E. Donnell Thomas, MD, helped in the management of this patient's condition.

Nonproprietary Names and Trademarks of Drugs

Allopurinol—*Zyloprim.*
Vincristine sulfate—*Oncovin.*

1. Hynes H, Silverstain M, Fawcett K: Spontaneous rupture of the spleen in acute leukemia. *Cancer* 17:1356-1360, 1964.
2. Knoblich R: Pathologic (so-called spontaneous) rupture of spleen in leukemia and lymphoma. *Mich Med* 65:105-110, 1966.
3. Ravich R, Reed C, Stephens F, et al: Spontaneous rupture of the spleen in acute myeloid leukaemia. *Med J Aust* 1:90-92, 1971.
4. Hyun BH, Varga CF, Rubin RJ: Spontaneous and pathologic rupture of the spleen. *Arch Surg* 104:652-657, 1972.
5. Karakousis CP, Elias EG: Spontaneous (pathologic) rupture of spleen in malignancies. *Surgery* 76:674-677, 1974.
6. Gafter U, Mandel EM, Weiss S, et al: Primary fibrinolysis and spontaneous rupture of the spleen in acute lymphoblastic leukemia. *Acta Haematol* 56:355-359, 1976.
7. Saiers J: Acute leukemia presenting as a ruptured spleen. *Rocky Mt Med J* 74:319-320, 1977.
8. Gibbs TJ, Sells RA, Bellingham AJ: A rare presentation of splenic rupture. *Postgrad Med J* 53:403-405, 1977.
9. Douglas GJ, Simpson JS: The conservative management of splenic trauma. *J Pediatr Surg* 6:565-569, 1971.
10. Howman-Giles R, Gilday DL, Venugopal S, et al: Splenic trauma: Nonoperative management and long-term follow-up by scintiscan. *J Pediatr Surg* 13:121-126, 1978.
11. LaMura J, Chung-Fat SP, SanFilippo AJ: Splenorraphy for the treatment of splenic rupture in infants and children. *Surgery* 81:497-501, 1977.

Doxepin Poisoning in a Child

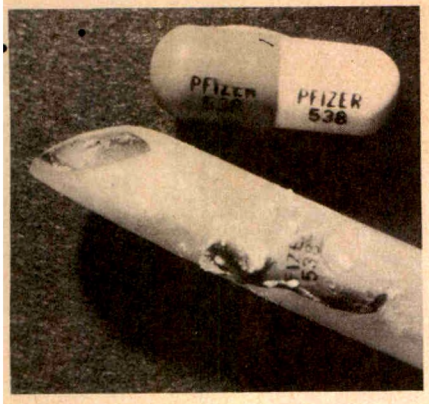
Tricyclic antidepressant drug overdose is an increasingly frequent cause of serious poisoning.[1] Imipramine and amitriptyline poisonings have been more commonly reported,[2-4] whereas the toxicity of doxepin, a newer drug of this class, is less well described.[5] We present a case of severe doxepin hydrochloride poisoning in a child who survived and in whom the diagnosis was made in an unusual and unexpected manner. To our knowledge, no case of doxepin poisoning in a child has been previously reported.

Report of a Case.—A 4-year, 6-month-old, 13-kg girl collapsed for no apparent reason after a morning of normal activity and was taken comatose to her local physician. A grand mal seizure ensued that progressed to status epilepticus during her transfer to the University of Kansas Hospital, Kansas City. The history obtained from the parents was negative for metabolic or seizure disorders. The parents did not suspect any drug or toxic chemical ingestion. On arrival at the hospital two hours after onset of her symptoms, the child was unresponsive to pain; her pupils were equally dilated and unreactive to light. She was having continuous seizures consisting of rapid twitching of the eyelids and extremities. Clinical observations were as follows: systolic blood pressure, 60 torr; respirations, 10/min and shallow; heart rate, variable at approximately 120 beats per minute; and rectal temperature, 36 °C.

Because of inadequate respiratory effort, the patient was intubated and given mechanical ventilatory assistance. Seizure activity persisted after administration of 10 mg of diazepam intravenously, but it was controlled with 100 mg of intravenous (IV) phenobarbital sodium. There was no improvement in the patient's condition after IV administration of naloxone hydrochloride, 0.06 mg, and 2.5 g of dextrose. Metabolic acidosis (pH, 7.27) and hypotension were rapidly corrected with adequate ventilation and appropriate IV fluids. Gastric lavage followed by intragastric instillation of activated charcoal was performed. The gastric contents had a bluish discoloration, but they contained no identifiable capsules or tablets. The child was given magnesium citrate three hours after the activated charcoal, but she did not have a stool. Bowel sounds ranged from decreased to absent.

During the initial intubation, a portion of a blue capsule was retrieved from the esophagus (Figure). The product identification number was legible, which allowed identification of the drug as doxepin (Sinequan), 100 mg. Thin-layer chromatography of an extract of the patient's urine verified the presence of unmetabolized doxepin and was negative for other drugs. When confronted with this information, the parents acknowledged having doxepin at home and later found 32 doxepin capsules along with 15 pentazocine hydrochloride tablets in a bottle under the patient's bed. The original quantities of each drug were unknown.

Based on the capsule identification, the patient was given physostigmine salicylate (1.5 mg) intravenously in three divided doses five minutes apart. Respiratory effort increased substantially, and her pupils became reactive to light; no other effects were observed. The body temperature remained below normal for the first five hours after admission, but then it became elevated for the next 24 hours. The child's respiratory effort and responsiveness to external stimuli improved during the second 12 hours of hospitalization, and she was extubated 20 hours after admission. She remained lethargic but responded to verbal stimuli and seemed to recognize her parents. Some 24 hours after admission, the patient was given two additional doses of physostigmine salicylate, 0.5 mg



Tip of endotracheal tube with adherent foreign material after attempted intubation. Capsule of doxepin (Sinequan) from patient's pill collection is shown for comparison.

each, after which she became much more alert, began talking, and passed a large charcoal stool.

The child's condition was evaluated by a cardiac monitor for the first five days of hospitalization, and no arrhythmias were detected at any time. The EEG and ECG were normal one week after admission. The patient remained ataxic for two days after admission, but this resolved and her neurologic examination showed no abnormalities ten days after the onset of symptoms.

Comment.—Ingestion of a toxin must always be included in the differential diagnosis of status epilepticus and coma in children. When the cause of the symptoms is not readily apparent, gastric lavage along with measures to inhibit further gastrointestinal (GI) absorption of a potential poison are mandatory parts of the emergency protocol. Pharmacologic screening of the urine or serum should also be a part of the evaluation of the patient. The drug imprint code on capsules or tablets, when available, can be an invaluable aid in arriving at a diagnosis. The present case dramatically illustrates these points.

Although this child had access to pentazocine in addition to doxepin, the clinical manifestations were most consistent with doxepin toxicity. The absence of pentazocine in the urine and the lack of effect by naloxone on respiration or level of consciousness also ruled out pentazocine ingestion. Respiratory depression, coma, and grand mal seizures are well-documented symptoms of a tricyclic antidepressant toxic condition. Hypotension, hyperthermia (which followed initial hypothermia), and dilated pupils are also characteristic.[2-4] In spite of these severe symptoms, the ECG of our patient, monitored continuously for five days, showed no evidence of cardiac arrhythmias or conduction abnormalities, which are frequently seen in tricyclic antidepressant overdose. This is consistent with the previously reported observation that although other tricyclic antidepressants alter intraventricular conduction, doxepin does not share this effect.[4,5]

Physostigmine has emerged as the cholinesterase inhibitor of choice in the treatment of life-threatening symptoms caused by the anticholinergic actions of the tricyclic antidepressants.[1,3,5,6] We observed a definite clinical improvement in this patient after administration of moderate doses of physostigmine salicylate (0.5 mg thrice, and later, 0.5 mg twice). Some authors have reported more aggressive use of physostigmine in cases of tricyclic antidepressant intoxication than was used for our patient; however, she recovered rapidly and completely with supportive care and cautious use of physostigmine.

Tricyclic antidepressants and their active metabolites undergo enterohepatic recycling and gastric secretion. Therefore, the administration of activated charcoal may speed the elimination of these compounds from the body.[1] In this patient, magnesium was ineffective in stimulating the movement of charcoal and adsorbed drug through the GI tract until physostigmine was administered. This complication of anticholinergic intoxication should be kept in mind when managing the conditions of such patients.

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Nonproprietary Name and Trademarks of Drug

Doxepin hydrochloride—*Adapin, Curatin, Sinequan.*

1. Manoguerra AS, Weaver LC: Poisoning with tricyclic antidepressant drugs. *Clin Toxicol* 10:149-158, 1977.

2. Goel KM, Shanks RA: Amitriptyline and imipramine poisoning in children. *Br Med J* 1:261-263, 1974.

3. Wright SP: Usefulness of physostigmine in imipramine poisoning: A dramatic response in a child resistant to other therapy. *Clin Pediatr* 15:1123-1128, 1976.

4. Biggs JT, Spiker DG, Petit JM, et al: Tricyclic antidepressant overdose: Incidence of symptoms. *JAMA* 238:135-138, 1977.

5. Janson PA, Watt JB, Hermos JA: Doxepin overdose: Success with physostigmine and failure with neostigmine in reversing toxicity. *JAMA* 237:2632-2633.

6. Rumack BH: Anticholinergic poisoning: Treatment with physostigmine. *Pediatrics* 52:449-451, 1973.

Recordkeeping and Physician Certification of Measles Immunization Status

The recent federally sponsored objective of achieving immunization levels of at least 90% in US children by 1979[1] is predicated on the assumption that all links in the chain of immunization recordkeeping are appropriately maintained, honestly evaluated, and fully reported. I report here an epidemic that demonstrates how these records can break down at two levels of reporting: the physician's office and the school.

Report of a Case. In February 1978, the Livingston County Health Department, Howell, Mich, received a school-initiated report that an open classroom elementary school with an enrollment of 512 students had eight cases of measles. The index case, an 8-year-old second-grader, was identified. We were unable to determine the index case's initial exposure; however, the potential for exposure was high as during this time in Michigan there were numerous outbreaks of measles in different communities around the state, including a large outbreak at one of the state's major universities in a county adjoining Livingston County.

This school had reported nearly perfect (99%) immunization compliance status for its entering children during the past two to three years. At the time, state law did not specify the minimum age for measles immunization.

In attempting to contain this outbreak, we reviewed the school immunization records of all 512 pupils to locate potentially susceptible children: those students who were not previously vaccinated or who were vaccinated at less than 13 months of age. The intent of the review was to notify only parents of susceptible children.

The results of our measles immunization status review of the 512 children were as follow:

1. Readily determined immunization information was available (*a*) for 24 (4.7%) children vaccinated before or at 12 months of age, (*b*) for 122 (23.8%) children vaccinated after 12 months of age, and (*c*) for 18 (3.5%) children not vaccinated.

2. No immunization records were pres-

ent in 81 (15.8%) children's school files, *or* the records were not completed.

3. Dates of measles immunizations in vaccination records were indeterminable for 255 (49.8%). (This includes two records marked "complete"; nine, "adequate"; and three, "up-to-date." Subsequent study showed that of the 348 students with incomplete, inaccurate, or nonexistent records, there were 138 who had not been adequately vaccinated.)

4. The students' files were not found for 12 (2.3%).

As is evident from this information, we were unable to determine the adequacy of immunization of 68.0% of the children. Hence, notes were sent to all children's homes requesting parents to reevaluate their children's measles vaccine status.

After the epidemic in the fall of 1978, a record review for all state-required immunizations was performed. Parents were contacted and asked to supply us with the month and year of measles immunization. After this contact, we found that an additional 210 of the children had been in compliance at the time of the outbreak, leaving 138 children inadequately immunized.

Comment.—To enhance the effectiveness and efficiency of communicable disease outbreak containment in institutional environments, complete and accurate records are a must. Because in this situation the records were difficult to interpret, we were forced to notify the entire population—an inefficient modus operandi.

The deficiencies in these school records were in four areas: (1) the school, which neither demanded the month and year of immunization nor excluded the noncompliant pupil; (2) the physician, who did not give the parents written records of their child's immunization history, who did not emphasize the necessity for the parent to keep the record permanently in good repair, or who supplied inadequate information on the written record; (3) the parent, who did not present the full information to the school when requested; and (4) the health department, which has not previously stringently enforced the school-entering law, thus assuring that a child's *reported* compliance is the *actual* immunization status of that child.

On at least two occasions when physicians who stamped "immunizations complete" or "immunizations adequate" on the school forms were contacted, we found that the children had not received measles immunization, a finding that has profound health and legal implications.

As in other areas of medicine, immunization standards of care are frequently changing, requiring precise medical histories for frequent reevaluation of vaccination status. The importance of age at vaccination for measles is just now being clarified. For many years, it was assumed that vaccination at age 12 months offered adequate protection, but recent studies showed that age-specific attack rates were substantially higher in those vaccinated before age 12 months.[2-6]

The debate on the necessity for revaccination of those children initially vaccinated prior to 13 months continues.[5-7] When, and if, this debate is resolved, physicians will have to work with the schools to assure the adequacy of our children's protection against vaccine-preventable disease. Without accurate records, this assurance is impossible. Furthermore, schools will be unable to comply with changing immunization rules and regulations if their current records are not complete.

The inadequacy of immunization care is not unique to private practitioners in a relatively rural area like Livingston County. Pope[8] has demonstrated less-than-optimal immunization standards in a health maintenance organization population, where he found that 12% of eligible children had not been vaccinated against measles. Moreover, about 50% of all school-age children cared for by this particular organization had not received one or more of the school-required immunizations.

Through complete physician cooperation, we can all help our patients meet the objectives of the national immunization initiative. Rigorous attention to immunization records can help to avoid large outbreaks of vaccine-preventable disease.

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Marilyn Lee, RN, MS, MPA, and Robert Scranton, RS, MPH, assisted in the record review. Larry Brilliant, MD, MPH, and James Koopman, MD, MPH, commented on this article.

1. Hinman AR: The childhood immunization initiative. Presented at the 106th Annual Convention of the American Public Health Association, Los Angeles, Oct 18, 1978.

2. Rawls WE, Rawls ML, Chernesky MA: Analysis of a measles epidemic: Possible role of vaccine failures. *Can Med Assoc J* 113:941-944, 1975.

3. Balfour HH Jr, Amren DP: Rubella, measles and mumps antibodies following vaccination of children: A potential rubella problem. *Am J Dis Child* 132:573-577, 1978.

4. Shasby DM, Shope TC, Downs H, et al: Epidemic measles in a highly vaccinated population. *N Engl J Med* 296:585-589, 1977.

5. Yeager AS, Davis JH, Ross LA, et al: Measles immunization successes and failures. *JAMA* 237:347-351, 1977.

6. Marks JS, Halpin TJ, Orenstein WA: Measles vaccine efficacy in children previously vaccinated at 12 months of age. *Pediatrics* 62:955-960, 1978.

7. Halsey NA, Nieburg PI, Preblud SR, et al: Effectiveness of measles vaccine administered at 12 months of age. Part of a presentation for the American Academy of Pediatrics Committee on Infectious Diseases (Red Book Committee), Atlanta, April 24, 1978 and for the Advisory Committee on Immunization Practices (ACIP), Atlanta, May 11, 1978.

8. Pope CR: The immunization status of an HMO population. Presented at the 106th Annual Meeting of the American Public Health Association, Los Angeles, Oct 18, 1978.

Symptomatic Hyponatremia in Nephrotic Syndrome

Hyponatremia may occur in children with nephrotic syndrome, usually when diuretic therapy has been used. Hyponatremia owing to inadequate salt intake, in the absence of diuretic treatment, is an unusual but probably overlooked cause.[1,2] We report our experience in caring for a 2½-year-old boy with steroid-responsive nephrotic syndrome who had disorientation and hallucinations as a result of severe hyponatremia.

Report of a Case.—A male infant had classical nephrotic syndrome at age 21 months. He responded within two weeks to oral prednisone (2 mg/kg/day), with resolution of the edema and disappearance of the proteinuria. The prednisone dose was reduced during the next several weeks until a clinical relapse occurred. Again, daily prednisone treatment induced a remission, and a course of alternate-day prednisone was planned. While taking 40 mg of prednisone every other day, he had proteinuria (4+) without edema and, four days later, the prednisone dosage was increased to 10 mg four times daily. No diuretic therapy was given. His weight was 17.3 kg and he did not appear swollen.

Five days later, he had edema and complained of abdominal discomfort. He had no fever, emesis, or diarrhea but was not eating well. The abdominal examination was consistent with moderate ascites; there were no signs of peritonitis. His weight was 19.5 kg, and he was alert and cooperative and was not in any distress. Vital signs, including blood pressure and temperature, were normal. He was admitted to the hospital for observation of possi-

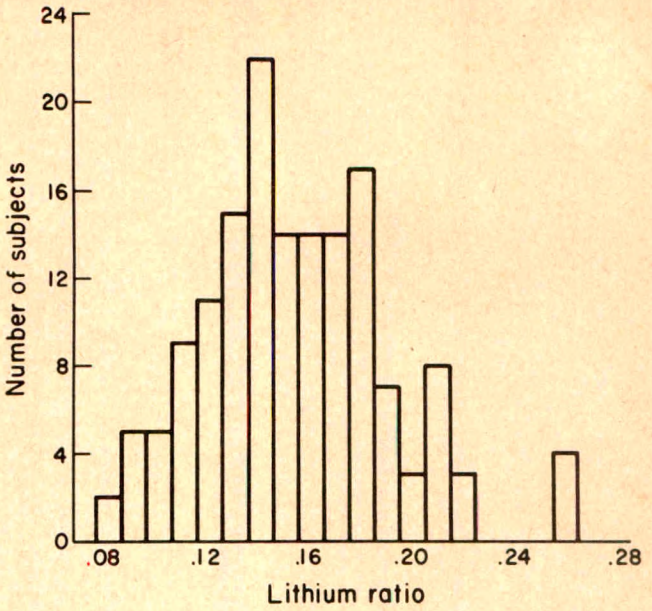
ble early peritonitis.

Laboratory studies showed the following values: initial serum electrolyte, severe hyponatremia (see Table); BUN, 38 mg/dL; creatinine, 0.7 mg/dL; albumin, 1.9 g/dL; and cholesterol, 602 mg/dL. Serum Na was repeated six hours later (110 mEq/L), and the laboratory reported that his serum was not visibly lipemic. He remained alert with normal vital signs but because of the severity of the hyponatremia, an intravenous (IV) infusion of 0.9% sodium chloride solution was begun at a rate of 40 mL/kg/day. He was not permitted oral fluids. Fifteen hours later, the serum concentrations were as follow: Na, 98 mEq/L; Cl, 77 mEq/L; K, 5.8 mEq/L; and osmolality, 241 mOsm/L. Simultaneously, he had become extremely agitated and was exhibiting inappropriate behavior (biting mother and staff) as well as hallucinating about the presence of bugs and insects on the walls of his room. There was no seizure activity and vital signs were normal.

Hypertonic (3%) saline solution was administered; 24 hours later, his serum Na value was 127 mEq/L, and he again was oriented. As a result of the IV fluids, a further increase in edema occurred and furosemide therapy was begun on the third hospital day. After 20 days of daily prednisone therapy, he again had a clinical remission (weight decreased to 17.3 kg, no proteinuria). Serum electrolyte values were as follow: Na, 140 mEq/L; K, 4.4 mEq/L; Cl, 104 mEq/L; and CO_2, 24 mEq/L.

Dietary history indicated that the patient's mother had kept him on a severely restricted salt diet continuously since the initial diagnosis of his condition. The diet consisted of no salty foods and no salt with cooking, as well as low-salt bread, ketchup, margarine, etc.

Comment.—Nephrotic syndrome is usually an easily recognizable condition characterized by edema, proteinuria (> 50 mg/kg/day), hyperlipidemia, and hypoalbuminemia. In the untreated state (ie, no diuretics), serum Na concentration is most often normal and osmolality is normal to slightly elevated. "Pseudohyponatremia" may occur when the elevated serum lipids decrease the serum water content. In this instance, serum is visibly lipemic and serum osmolality, the measurement of which is unaffected by lipidemia, is not decreased.[3] In our patient, the serum osmolality was decreased, and although the serum cholesterol level was 602 mg/dL, the serum did not appear lipemic. Furthermore, no vomiting or diarrhea had occurred to account for an external loss of Na. The urinary Na concentration was negligible, indicating an appropriate Na-retaining state and thus not suggesting aldosterone deficiency, syndrome of inappropriate secretion of antidiuretic hormone, or salt-losing renal disease as explanations for this hyponatremia. Hyperglycemia is another cause of hyponatremia,[4] but there was no evidence for this in our patient.



The most reasonable explanation for this youngster's hyponatremia is a deficiency of dietary salt combined with the dilutional effect of his 2.3-kg gain in body water. The reason for the continued decrease in serum Na while he was receiving a small amount of 0.9% sodium chloride solution intravenously and in the absence of any substantial salt losses, is not clear. However, it is possible the "fall" in serum Na from 112 to 98 mEq/L was not real but due to the lipidemia. This would be consistent with the serum osmolality (241 mOsm/L), which was higher than the Na (98 mEq/L) and BUN (39 mg/dL) values would suggest. The initial elevated BUN and hemoglobin values are consistent with intravascular contraction, but there never were any other signs of hypovolemia to suggest this played a role in his disorientation.

Since minimal-change nephrotic syndrome is often a prolonged and frequently relapsing condition and since many families will embrace a "salt-free" diet as easier to follow routinely rather than only during periods of edema, it is important to emphasize the danger of too severe salt restriction. Salt restriction is not indicated during periods of clinical remission and should not be encour-

Laboratory Results and Some Clinical Values During Hospitalization

	Hospital Day*			
	1	2	3	4
Urine				
Na, mEq/L	...	1	2	3
K, mEq/L	...	49	70	36
Serum				
Na, mEq/L	112;110	98;116	127	127
K, mEq/L	6.2	5.8;4.9	5.4	4.3
Cl, mEq/L	82	77;90	105	106
Osmolality, mOsm/L	...	241;247	...	...
Hemoglobin (hematocrit), g/dL (%)	18.5 (54.6)	14.5 (42.4)	...	...
Fluid intake, mL	177	1,080	768	678
Urine, mL	141†	294	838	479
Weight, kg	19.5	20.4	20.7	20.6

*Numbers after semicolons indicate second set of values for days designated.
†Loss of some urine during collection period.

aged. A 2-g Na diet (no added salt diet) should provide sufficient restriction during the periods of clinical relapse and edema.

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1. Metcoff J, Janeway CA: Studies on the pathogenesis of nephrotic edema with particular emphasis upon changes in renal hemodynamics and the metabolism of electrolyte and proteins. *J Pediatr* 58:640-685, 1961.

2. Hagge WW, Burke EC, Stickler GB: Sudden death in the nephrotic syndrome: Salt depletion as a probable mechanism. *Clin Pediatr* 6:524-527, 1967.

3. Albrink MJ, Hald PM, Man EB, et al: The displacement of serum water by the lipids of hyperlipidemic serum: A new method for the rapid determination of serum water. *J Clin Invest* 34:1483-1488, 1955.

4. Carroll HJ, Oh MS: Electrolyte physiology and body composition, in *Water, Electrolyte and Acid-Base Metabolism: Diagnosis and Management.* Philadelphia, JB Lippincott Co, 1978, p 15.

Autoimmune Thyroiditis With Thyrotoxicosis Eventuating in Hypothyroidism in a Short Interval

Autoimmune thyroiditis may appear as thyrotoxicosis,[1,2] but it usually leads to hypothyroidism, although that evolution may take years.[3-6] We describe a 14½-year-old girl whose condition was in the thyrotoxic phase, who required antithyroid drugs, and who became hypothyroid in three months. The shortest interval previously described was six months.[5]

Report of a Case.— This 14½-year-old girl was admitted to the hospital with complaints of malaise, weight loss, sore neck, and mild fever of one week's duration, preceded by cough and rhinitis. Three days prior to admission, tender swelling was noted in the anterior side of the neck. On admission, she had a temperature of 38.9 °C, a pulse rate of 120 beats per minute and a blood pressure of 120/80 mm Hg. Her skin was warm and moist. The thyroid gland was threefold enlarged, soft and rubbery in consistency, and nontender, without local inflammatory signs. No thyroid nodules or regional nodes were noted. A bruit was present over both lobes of the thyroid gland. She was complaining of pain in the anterior side of the neck, radiating to the right ear. No eye abnormalities or tremor were seen, and deep tendon reflexes were normal. Family history showed no thyroid disease or autoimmune diseases.

White blood cell count was 7,000/cu mm. The ESR was 15 mm/hr; serum T_3 uptake was 47.3% (normal, 25% to 35%); T_4 value was 15.3 μg/dL (normal, 5 to 13.7); free T_4 index was 23.4% (normal, 4.4 to 15.7%); radioactive iodine uptake was 20% at 4.5 hours and 27% at 24 hours, without discharge by $KClO_4$, which was given at 4.5 hours. Antithyroglobulin antibody titer was 1:10 (normal, < 1:20). Antimicrosomal antibody titer was 1:25,600 (normal, < 1:100).

She was given aspirin (acetylsalicylic acid) at 60 mg/kg/day for 3.5 weeks. Propranolol hydrochloride, 160 mg daily, divided in four doses, was started on the second hospital day when she had increasing enlargement of the thyroid gland, bounding pulse, an aortic insufficiency murmur, and blood pressure of 140/50/0 mm Hg. Because of development of an allergic rash, propranolol therapy was discontinued three weeks later, and she was given propylthiouracil, 150 mg every eight hours. Five weeks later, she was clinically euthyroid. Propylthiouracil therapy was discontinued at three months of treatment because of suspicion of hypothyroidism. The thyroid gland was still twofold enlarged.

Two months later (six months after onset of disease), she returned complaining of tiredness, poor appetite, and generalized puffiness of one week's duration. She had cool, dry skin, a puffy face, and increased supraclavicular fat pads. The thyroid gland was not enlarged. Laboratory findings were as follows: serum T_3 uptake, 23.9%; T_4, less than 2.0 μg/dL; free T_4 index, less than 2.0%; TSH, 50.7 IμU/mL. She was given levothyroxine sodium (L-thyroxine), 0.25 mg daily.

After 15 months of treatment, levothyroxine was discontinued to assess her thyroid status. Thyroid tests were repeated six weeks after treatment was discontinued with the following results: serum T_3 uptake, 27.7%; T_4, 10.0 μg/dL; free T_4 index, 11.4%; TSH, 3.7 IμU/mL; antithyroglobulin antibody titer, 1:640; antimicrosomal antibody titer, 1:6,400. Her thyroid gland was of normal size and soft in consistency when we saw her again three months after treatment was discontinued. She remained clinically euthyroid.

Comment.—The diagnosis of autoimmune thyroiditis was made on the basis of an elevated antibody titer.[7] Such high antibody titers would be unexpected in classical Graves' disease, but they are associated with lymphocytic infiltration of the thyroid gland.[8]

The tests that should differentiate subacute from chronic lymphocytic thyroiditis gave conflicting information. The radioactive iodine uptake was greater than would be expected for subacute thyroiditis[1] although the tender gland and pain referred to the ear suggested that condition. However, radioactive iodine was not discharged from the gland when potassium perchlorate was given, as would be expected in autoimmune thyroid disease.[7] In the absence of histological confirmation, the diagnosis of Hashimoto's thyroiditis in this patient cannot be considered established. However, the clinical course, although accelerated, is in keeping with lymphocytic thyroiditis.

When subclinical hypothyroidism was suspected after three months of propylthiouracil treatment, we had to differentiate propylthiouracil toxicity from spontaneous development of hypothyroidism. Hypothyroidism secondary to propylthiouracil usually lasts only for a few weeks and is accompanied by an enlarging thyroid gland. But two months later, the previously enlarged thyroid gland was barely palpable, suggesting spontaneous development of hypothyroidism.

The course in this patient is unusual in that transient hypothyroidism followed thyrotoxicosis in so short a period of time. This sequence of events calls attention to the necessity of maintaining close contact with patients who have thyroiditis.

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This work was supported in part by grant number 5T32 HDO 7053 from the National Institutes of Health.

1. Gluck F, Nusynowitz M, Plymate S: Chronic lymphocytic thyroiditis, thyrotoxicosis, and low radioactive iodine uptake. *N Engl J Med* 293:624-628, 1975.

2. Mäenpää J: Juvenile goitrous autoimmune thyroiditis. *Acta Pediatr Scand* 61:49-62, 1972.

3. Doniach D, Hudson RV, Roitt IM: Human autoimmune thyroiditis: Clinical studies. *Br Med J* 1:365-373, 1960.

4. Gordin A, Lamberg B: Natural course of symptomless autoimmune thyroiditis. *Lancet* 2:1234-1280, 1975.

5. Nilsson L, Doniach D: Autoimmune thyroiditis in children and adolescents: I. Clinical Studies. *Acta Pediatr* 53:255-268, 1964.

6. Saxena KM, Crawford JD: Juvenile lymphocytic thyroiditis. *Pediatrics* 30:917-926, 1962.

7. Fisher DA, Oddie TH, Johnson DE, et al: The diagnosis of Hashimoto's thyroiditis. *J Clin Endocrinol* 40:795-801, 1975.

8. Sato T, Takata T, Taketani T, et al: Concurrence of Graves' disease and Hashimoto's thyroiditis. *Arch Dis Child* 52:951-955, 1977.

Necrotizing Enterocolitis

Sir.—I read with interest the article "Epidemic Occurrence of Neonatal Necrotizing Enterocolitis," by Guinan et al (JOURNAL 133:594-597, 1979). The observation that almost all infants (38 of 39) were fed prior to the onset of necrotizing enterocolitis (NEC) is in agreement with other studies.[1-5] In one retrospective, case-control study similar in design to that of Guinan et al, 54 of 54 infants were fed prior to NEC onset, whereas only 63% of 98 matched controls ($P < .001$) were fed at a comparable time.[2] These findings strongly suggest an etiologic relationship between feeding and NEC. Guinan et al do not tell us how many of their controls were fed, and this would be a statistic of some interest.

In an unpublished survey carried out in the early 1960s of feeding practices in six premature nurseries in the metropolitan New York City area, I found that slow, gradual feeding increments were the rule; also, that the feeding of premature babies was generally regarded as an important and difficult task that required considerable knowledge and experience. A senior nurse with a special interest in feeding often had the responsibility for ordering feeding volumes. The infant's size, age, clinical status, and especially his tolerance to feedings all entered into the feeding equation. Now, in our modern, very complex neonatal units, there has been, I fear, a downgrading of the importance of feeding and, at times, assignment of this responsibility to inexperienced personnel. In addition, concern with regard to possible (but unproved) effects of undernutrition on the developing brain has created an urgency to increase caloric intake. In this climate, it should not be surprising that epidemics of NEC may occur. Indeed, it may very well be that the outbreak of NEC in the United States since the mid-1960s is itself an epidemic that has resulted largely from a radical change in the manner in which we feed our premature infants. The current situation is reminiscent of that with pellagra in the early part of this century. Pellagra, like NEC, occurred in institutional epidemics and there were many who believed the disease to be infectious.[6]

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1. Santulli TV, Schullinger JN, Heird WC, et al: Acute necrotizing enterocolitis in infancy: A review of 64 cases. *Pediatrics* 55:376-385, 1975.
2. Frantz ID, L'Heureux P, Engel RR, et al: Necrotizing enterocolitis. *J Pediatr* 86:259-263, 1975.
3. Roty AR, Kilway JB, Brown AL: Acute necrotizing enterocolitis in neonates. *Am Surg* 43:392-394, 1977.
4. Bell RS, Graham CB, Stevenson JK: Roentgenologic and clinical manifestations of neonatal necrotizing enterocolitis. *Am J Roentgenol Radium Ther Nucl Med* 112:123-127, 1971.
5. Krouskop RW, Brown EG, Sweet AY: The relationship of feeding to necrotizing enterocolitis, abstracted. *Pediatr Res* 8:383, 1974.
6. Terris M: *Goldberger on Pellagra.* Baton Rouge, La, Louisiana State University Press, 1964, pp 10-11.

In Reply.—I agree with Dr Goldman that the relationship between changed feeding patterns for premature infants and the increased incidence of neonatal NEC is striking. Unfortunately, we were unable to study feeding patterns within each hospital before and during the epidemics for evidence of significant change. In our studies, only two of the 53 control infants were not fed within a time period comparable to that of case infants. The number of infants fed within 24, 48, or 72 hours of birth did not differ between the two groups, nor did the number of infants who received their first oral feeding after the fifth day of life. We were able to compare the average daily mean volume of formula received by case and control infants during the first five days of life only in hospital C, and found no significant difference between the two groups.

Book et al[1] showed that carbohydrate malabsorption preceded the development of NEC in affected infants, and that control infants had significantly less evidence of a carbohydrate malabsorption. Carbohydrate overloading of the absorptive capacity of the newborn intestinal tract and consequent passage of the carbohydrate to the lower intestinal tract could provide gas-forming bacteria with increased substrate for gas production. If infants are unable to absorb or expel the gas, the buildup of gas pressure may be sufficient to cause pockets of intestinal necrosis. Thus, at least three conditions would be hypothetically necessary for development of disease: (1) carbohydrate in the colon, ileum, or jejunum; (2) colonization of these areas with gas-forming bacteria; and (3) either impairment of intestinal motility that prevents expelling the gas or inability of the intestine to absorb the particular gases formed.

The histopathology of NEC, with notable lack of polymorphonuclear leukocytes, is not consistent with a colitis, but with a pressure necrosis.[2] Areas of necrosis do not follow a vascular pattern and are often bound by areas of apparently normal intestinal tissue. Perhaps the disease would be more appropriately named "necrotic gut syndrome of the newborn," and this change in concept might alert investigators to search for causes other than causes of colitis in this syndrome. Dr Goldman's suggestions are timely and provocative, and are greatly appreciated.

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1. Book LS, Herbst JJ, Jung AL: Carbohydrate malabsorption in necrotizing enterocolitis. *Pediatrics* 57:201-204, 1976.
2. Santulli TV, Schullinger JN, Heird WC, et al: Acute necrotizing enterocolitis in infancy: A review of 64 cases. *Pediatrics* 55:376-386, 1975.

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.
PRECAUTIONS: If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.
Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.
ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

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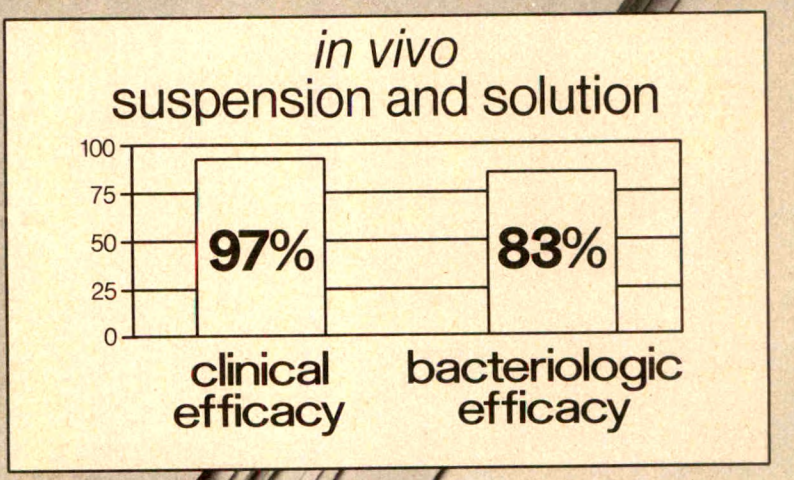

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* Cassisi N, Cohn A, Davidson T, et al: Diffuse otitis externa: Clinical and microbiologic findings in the course of a multicenter study on a new otic solution. *Ann Otol Rhinol Laryngol* 86(suppl 39, pt 3):1-16, 1977.

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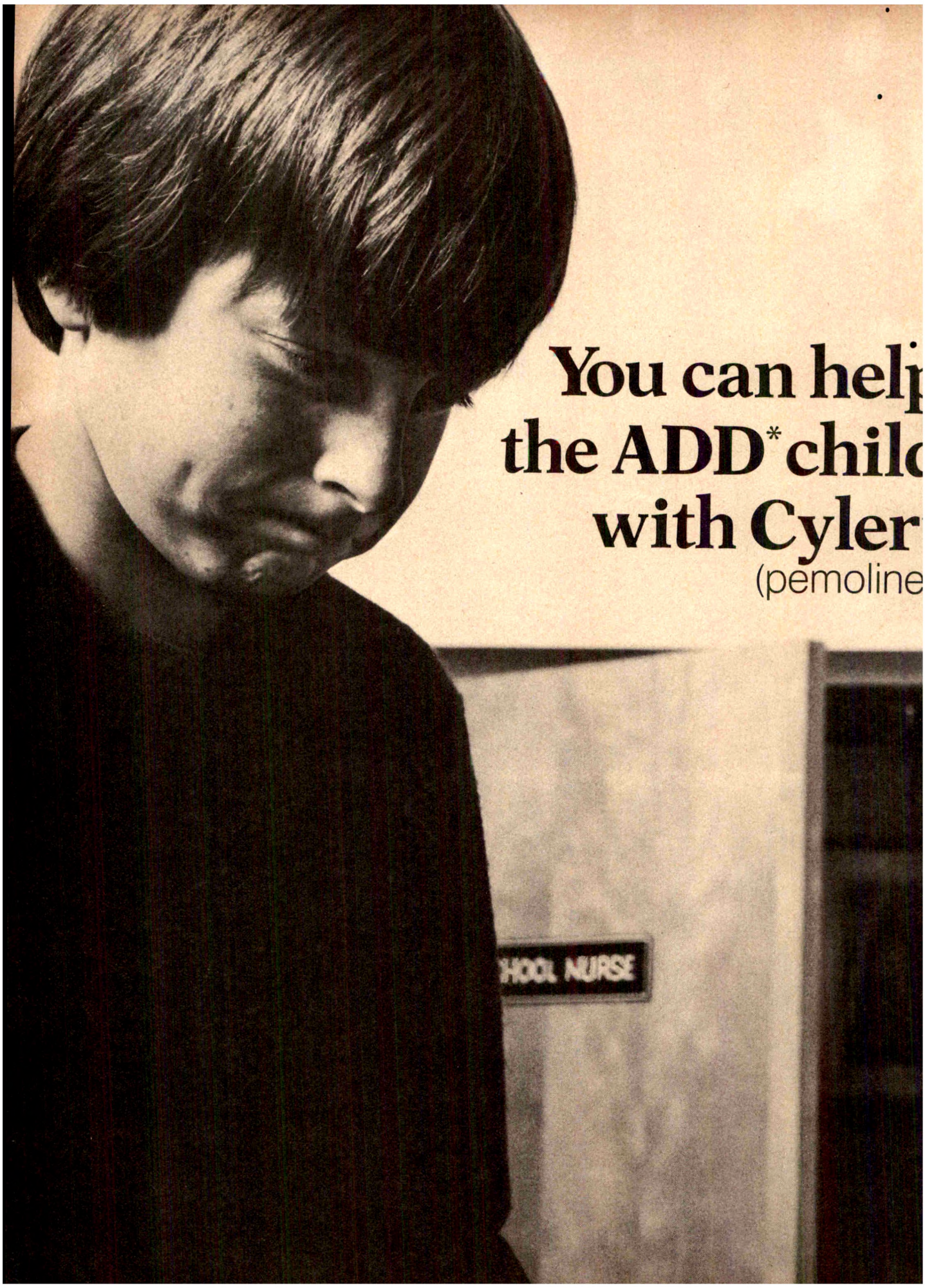
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DESCRIPTION: CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one.

Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg./ml.) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg./ml.

CYLERT (pemoline) is supplied as tablets for oral administration.

CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

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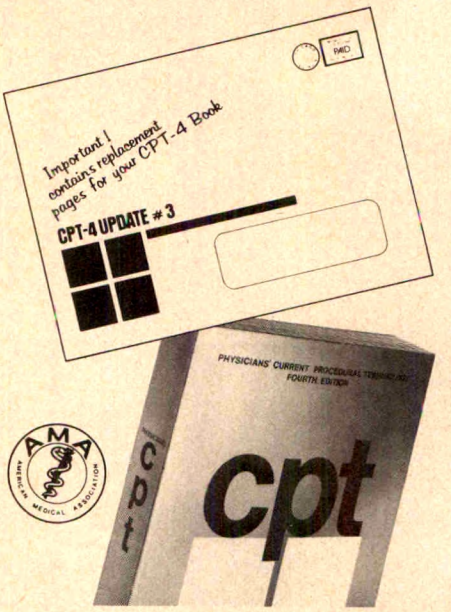

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Books

Fetal Growth in Humans, by Herbert C. Miller and Allen Merritt, 180 pp, Chicago, Year Book Medical Publishers Inc, 1979.

This book reports the findings of an exhaustive five-year study made personally by the authors. The main objectives of the study were as follows: (1) to construct standards for presumably normal fetal growth from anthropometric data of newborn infants who were "free from all known growth retarding influences in utero"; (2) to expand the number of atypical fetal growth patterns presently being recognized and to compare infants with these atypical patterns against the normal standards; and (3) to describe the causes and consequences of atypical fetal growth.

The authors thus set themselves a formidable task, and it would have been impossible to satisfy all their potential critics. Most clinicians and research workers in this field would agree that the criterion of slow fetal growth in terms of weight for gestational age at birth is not entirely satisfactory. But it has, at least, the advantages of general acceptance and simplicity. This allows for comparisons between studies made in different populations and under varying conditions. It is also still possible, within groups of small-for-date (or large-for-date) babies ascertained by a weight criterion, to subcategorize them according to their length and/or head circumference measures and thus to take account of their heterogeneity. Statistical validation is important if different patterns of atypical fetal growth are categorized ab initio by indices comprising two interdependent variables.

The control group on which the anthropometric data on normal infants were obtained was a highly selected sample since two of every three full-term infants and about 85% of all premature infants were excluded because of "some fetal or maternal growth-retarding factor." Among the latter, particular emphasis was paid to a group of maternal "behavioural conditions" that the authors consider modifiable and largely a matter of maternal choice. As well as smoking, drug addiction, and excessive alcohol consumption during pregnancy, factors such as delivery before the 17th or after the 35th birthday, lack of antenatal care, low weight gain during pregnancy, and low prepregnancy weight for height were also included in this "behavioural" group. However, short stature and very low prepregnancy weight, alone, were not considered growth-retarding factors at all. The only growth-accelerating factors that prompted exclusion from the control group were gestational diabetes and diabetes mellitus, and no account was taken of the large biological variations in size at birth. The arbitrary nature in which some factors were included or excluded does not lend credibility to the findings based on comparisons within and between the groups.

Despite the aforementioned reservations, this book is packed with a large amount of useful and interesting information, and it gives a refreshing new look at a subject that has been the basis of intense investigation during the last ten to 15 years. There is an interesting chapter on twin pregnancy; and the observation that, among control infants, the incidence of small head circumference was 0.8% for obese mothers, compared with 9.7% for slender mothers and 8.7% for underweight mothers has important implications for sonographers who judge fetal size and maturity by BPD techniques.

Clinicians and research workers interested in somatic growth will all find something new, or provocative, in this book. However, I doubt whether many will actually want to own it.

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Abnormal Fetal Growth: Biological Bases and Consequences, edited by Frederick Naftolin, 289 pp, $11.95, Berlin, Dahlem Konferenzen, 1978.

The provenance of this book was a Dahlem workshop held in West Berlin in February 1978. Unlike most symposia, no lectures were given. Selected participants were asked to write background articles providing a review of their own particular aspect of the subject. These were intended to be provocative as well as informative. They were circulated to the other participants and questions formulated before the meeting so that detailed discussions could begin, forthwith.

It is clear that the participants were carefully chosen and that each was of high repute in his own discipline. They ranged from cell biologists, embryologists, experimental physiologists, and agriculturalists to research workers and clinicians working mainly in obstetrics and pediatrics.

The structure of the workshop was such that after the opening plenary sessions, four separate groups were formed to discuss different aspects of the subject. Each group presented a report at the end of the meeting. The structure of the book follows this patten and reflects the intensive thought and intellectual activity generated.

The 11 background articles in this book are all of a high standard. Long lists of references are not given. Instead, care has been taken to quote the most relevant and pertinent. Apart from a few classics such as Walton and Hammonds' well-known crossbreeding experiments, they report work mainly done in the present decade.

The first section is the "Definition, Epidemiology and Identification of Abnormal Fetal Growth." The background works on concepts and criteria and on present methods of intrauterine diagnosis are concerned primarily with human beings, and the essential points that emerged in discussion are outlined in the group report. (D. Hull, rapporteur). A brief resume of pathological factors is given, but emphasis was mainly directed to biological phenomena. Among maternal factors, the concept of maternal constraint is discussed, and it is explained that, in this context, it is used to mean that characteristic transmitted by the mother to her daughters that influences the fetal growth of all her young of both sexes and that is transmitted through the female line. The concept of "brain sparing" was considered and the group concluded that if the expression were not so firmly entrenched, they would have recommended that it be dropped. "As it is, it must be more realistically described in order to avoid any of the optimism it often engenders." This group pointed out that the most important consequence of abnormal fetal growth is its long-term, even postnatal effects; and they suggested that perhaps this should be the yardstick by which we judge the influences that produce abnormalities in fetal growth, or the interventions that are aimed at preventing them.

However, postnatal consequences were not within the remit of this workshop. It is hoped that a subsequent one will be convened to consider them.

The second section is concerned with early development, and includes works on experimentally induced chromosome aberrations, mechanisms of embryonic organ formation, and the importance of growth factors. The group report (P. W. Nathanielsz, rapporteur) analyzes the various basic mechanisms as an ordered sequence: prezygotic, peri-implantation, organogenesis, and maturation. It seems that synchronization between embryo and maternal organism may be the primary focus of action for many of the genetic and environmental factors that were discussed; and the group concluded that a better understanding of the basic mechanisms is an essential prerequisite to control and possible therapy in prenatal and postnatal life.

The last two sections of the book are concerned with fetoplacental growth, and they describe wide-ranging studies on other mammals (rats, rabbits, guinea pigs, sheep, rhesus monkeys, and chickens, etc). The background articles explore the factors regulating the growth of the placenta, deviations in organ growth and maturation, substrate availability, enzymes, and the regulation of placental blood flow and oxygen transfer in relation to fetal growth. There is also a salutary chapter by K. Benirshke on the relevance of comparative studies in animals. The third group report (J. R. G. Challis, rapporteur) gives a summary of our present knowledge about the main influences, interactions, and mediating factors affecting placental and fetal growth. The final report (F. D. Frigoletto, rapporteur) considers in depth the many areas of ignorance that still exist, including cautionary tales, the problems of "animal models," the fetoplacental unit as a two-way process, and the question of therapy for the growth-retarded fetus. Some worthwhile research directions are outlined.

In recent years, there have been a number of publications reporting the proceedings of symposia on the subject of fetal growth. This is the best yet. It reflects five days of intensive discussion and integration by a multidisciplinary international group of experts. This is condensed into one volume. The contents would be of interest to all practising obstetricians and pediatricians. The large number of research workers in this field will find it compelling reading, and they are well advised to have a copy of their own.

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Atlas of the Newborn, by Neil O'Doherty, 412 pp, 530 illus, $29, Philadelphia, Harper & Row Publishers Inc, 1979.

The old chestnut that a picture is worth 1,000 words would surely justify the publication of a color atlas of the newborn. The explosion of knowledge on the care of the neonate has reached the encyclopedic state, with each new volume exceeding the previous one in a mass of verbal detail. Thus, a text that depicts visually the essentials of neonatology would be most welcome. To that end, Neil O'Doherty of the University College of Dublin has assembled more than 500 color photographs and has authored a succinct accompanying text. The result is an atlas of the newborn that emphasizes the physical characteristics of the newborn, both normal and abnormal.

The *Atlas* is organized into six separate and roughly equal sections, entitled: "The Normal Infant and His Trivial Complaints," "Low Birth Weight Babies," "Trauma," "Infection," "Congenital Abnormality," and "Skin Defects." The great majority of the photographs are of physical signs, and only a rare roentgenogram or a surgical or pathological specimen is presented.

From a technical point of view, by and large the *Atlas* succeeds. The quality of the color photography exceeds that found in most textbooks, both in clarity and in color reproduction. This is especially true in the chapter on skin defects. As to content, however, serious deficiencies exist. This is most glaring in the section on infection and congenital anomalies. Diseases with classic external physical characteristics, such as syphillis and herpes, are not pictured at all, whereas others are given short shrift. Similarly, whereas trisomy 21 is pictured with all its characteristic features, most other chromosomal entities either are not pictured at all or are incompletely presented. Thus, as a guide for the clinical evaluation of congenital abnormalities, this section pales in comparison to Smith's classic text *Recognizable Patterns of Human Malformation,* or even the short *Atlas of Mental Retardation Syndromes* of Gellis and Feingold.

The strongest chapters are those that picture the newborn infant with all his normal and minor variations. As a guide to the inexperienced student or physician learning physical diagnosis, this section is unrivaled. Surprising, however, is the unsystematic approach to the presentation of the low birth weight infant. Conspicuous by its absence is a pictorial representation of the features of Dubowitz's examination. In contrast, whereas the section on birth trauma is quite vivid and emphasizes the variety of iatrogenic insults that are inflicted on the newborn, one must wonder why there was need to present 14 different pictures of cephalohematoma. This disproportion between the number of pictures and the incidence or seriousness of the physical defect is quite common. Even less successful, in general, is the accompanying text. It is all too often too detailed for a commentary on the pictures and inadequate as a textbook of neonatology.

The general spottiness of the material presented suggests that the contents of the *Atlas* were determined by the available illustrations, rather than the converse method of choosing the subject matter and then seeking the appropriate photographs. As a result, the *Atlas,* while offering a series of superb photographs at a very reasonable price, cannot be recommended as a critical part of the pediatrician's library.

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Adolescence, by Doris Odlum, 162 pp, $10.50, Westport, Conn, Technomic Publications Inc, 1979.

Adolescence is the critical period of human development that encompasses the physical and psychological changes transforming the child into the adult. Though the preface indicates that this book is written for anyone, it seems to be an overview of this process of adolescence for parents of teenagers. It was first published more than 20 years ago under the title *Journey Through Adolescence,* and indeed it watchfully takes

the reader through the Alice-in-Wonderland evolution of the child into the adult. It was written by a psychiatrist, who uses principles of adolescence along with brief personal cases and literary quotations to clarify her discussions. Theories of adolescence are translated into practical explanations of why a teenager does specific, seemingly bizarre actions, so that parents can try to understand their own or other teenagers. Dr Odlum mixes in a delightful personal seasoning, based on much experience with, and obvious enjoyment of this age group.

The book is divided into 15 sections that cover many aspects of youth, including health, home, school, employment, friendships, cognitive thinking, and moral values. Concepts of adolescent sexuality are covered throughout the book, but there are specific sections on "adolescent pleasures," masturbation, sex, "love," and homosexuality.

There are many comments that parents will find valuable and even reassuring in this book. Parents will especially note Dr Odlum's emphasis on a stable home with a good parental marriage, and her view that despite the complex turmoil of adolescence most emerge intact from their teenager years. Also covered are the concepts of teenage ambivalence, magical thinking of teens with regard to their own sexuality, the differences in male and female sexual responses, and the need of youth for some limits.

There are good discussions of the need to treat each teenager individually, the oft-noted parental concern with their teenager's friends ("good vs bad"), the problem of sibling rivalry, the normal guilt feelings of parents who have a handicapped child, and even the difficulty of dealing with education and employment in an increasingly specialized environment. Parents will also read with great interest the explanations given for the loud teenage music, their hysterical reaction to rock stars, and even the "mod" teen dress phenomenon. The section on masturbation is interesting, as parents are told it may play a useful role in teenagers lives by the reduction of sexual tension.

However, the question remains whether or not this book is useful for the pediatrician seeking careful documentation of the process called adolescence. I think not. The medical advice tends to be spotty, occasionally inaccurate and often not tightly described. Girls are advised not to go swimming while menstruating, and acne is related to overactive sebaceous glands with dust settling in enlarged pores. It is stated that there are almost no physical illness teenagers are prone to develop. Constipation and foot disorders are singled out for discussion in this light. Parents are advised to be concerned about their teenager's bowel habits. There is no mention of Tanner staging, physiologic leukorrhea, and many other important medical concepts.

A discussion of menstruation does not mention that many girls view menarche as a venereal disease or as evidence of injury. Fathers are told that they are shy about telling their teenage daughters sexual information, but not of the normal Oedipal distancing that occurs between them. Theories of adolescence are not presented in enough detail and not identified as to their origins. Established theory and opinion become merged. Many of the comments apply to middle-class teenagers in England and are not always transferable to other groups.

Finally, I do not mean to be overly critical. This book presents a colorful and worthwhile overview of adolescence for parents, and for pediatricians who are parents of teenagers and who wish to enjoy a book from that perspective. If the physician wishes to have information about the sphere of adolescent medicine that will provide critical information that has been peer-reviewed and will aid in a professional evaluation and treatment of teenaged patients, there are other references to use. Adolescent medical literature is growing, and *carefully* detailed works are needed.

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Atlas of Clinical Conditions in Pedodontics, by R. Rapp and G. B. Winter, 142 pp, 478 illus, Chicago, Year Book Medical Publishers Inc, 1979.

This atlas is a collection of clinical photographs and roentgenographic illustrations of pathologic conditions that involve the oral cavity, face, and cranium. Covered are hereditary disorders, developmental problems, infectious diseases, trauma, neoplasms, and the volume includes a variety of pictures that demonstrate the limits of normality. The authors are well-known, highly respected pedodontists. Although this book might be of greater interest to dentists, it could be of value to the pediatrician confronted with a pathologic oral condition.

The 478 illustrations are nicely reproduced, with reasonably accurate color rendition of the tissues involved. The roentgenograms have been duplicated clearly and should be readily understood even by those not familiar with intraoral roentgenograms. The authors have chosen to depict most of the commonly occurring conditions seen by the clinician. They have also included several rarer conditions, such as trisomy 13-15 syndrome and oculoauriculovertebral dysplasia. In most cases, the illustrations depict a representative example of the disease as it is usually seen. In a few instances, a severe or unusual manifestation is illustrated.

The book is divided into sections that deal with the cranium and face, the teeth, gingiva, oral mucosa, palate, tongue, jaws, and limbs. This last section depicts conditions related to oral pathology or referred to in the earlier sections (thrombocytopenia, syndactyly, osteogenesis imperfecta, etc). The nomenclature used is familiar, and the British spellings are only a mild distraction.

The *Atlas* is not intended for use as a textbook. Written descriptions are concise and limited to a brief history or explanation of the condition. No attempt is made to explain treatment options or prognosis. The organization of the book into "anatomic" sections makes it easier to use as a reference to help establish a diagnosis. This atlas compares favorably to others that deal with oral pathology and pedodontics, and will be of special interest to those devoted to the health care of children.

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Perinatal Coagulation, by William E. Hathaway and John Bonnar, 235 pp, $17.50, New York, Grune & Stratton Inc, 1978.

The specialty of perinatology has blossomed and burgeoned during the past few years and has brought together a health team of obstetri-

cians, neonatologists-perinatologists (nepediatricians), clinical nursing specialists, and technicians whose primary concern is the pregnant mother and her newly born infant. This symbiotic unit has special medical problems, and a firm understanding of the physiology and pathophysiology of interacting systems has obvious merit for those charged with its care. Thus, it is appropriate that two authorities in the field, Dr William Hathaway, a pediatric hematologist whose major contributions have been in the field of neonatal coagulation, and Dr John Bonnar, an obstetrician-gynecologist with a particular interest in hemostasis during pregnancy, have collaborated in preparing this interesting monograph. A common problem in any perinatal center today is the 1,100 g premature infant with respiratory distress syndrome and ecchymoses, oozing from puncture sites, thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), decreased fibrinogen level, raised levels of fibrin split products, and decreased activities of factors II, VII, IX, X, and XII. Similarly, obstetrical patients with life-threatening massive hemorrhage and deep-vein thrombosis, and pulmonary embolism will tax the clinical skills of most physicians.

The problem with perinatal medicine is partly political and partly intellectual. As an independent administrative unit, divisions of perinatology have become liberated from their parent department of pediatrics. In some units, less rather than more interaction with pediatric subspecialists (eg, hematologists, cardiologists) has evolved with the self-recognition of the perinatologist-neonatologist as the "compleat pediatrician." Drs Hathaway and Bonnar state in the preface that the purpose of their new textbook is to synthesize the state of the art of perinatal coagulation for the "clinicians responsible for the care of the mother and her infant." Although it is unlikely that the same clinician treating deep-vein thrombosis and pulmonary emboli in a 32-year-old primigravida would write orders for the 1,100 g infant with disseminated intravascular coagulation (DIC) described earlier, the aim of this textbook is to unite the study of coagulation, normal and abnormal, occurring in the perinatal period. In providing an overview of the normal physiology of coagulation and the associated clinical disorders, the authors perform a creditable service. The hematologist, who should be consulted about major bleeding problems, will find that other available textbooks cover the physiology of coagulation in much greater detail and provide the required information to diagnose and manage these problems.

If the purpose of the book is to educate the obstetrician and the neonatologist, it will do an admirable job. The most fascinating reading concerns those states of intravascular coagulation in the mother or in the fetus that can cause similar changes in the other, eg, retained dead fetus or placental abruption. Similarly, the relationship between anticoagulation therapy in the mother and the fetus are well covered (eg, heparin does not cross the placenta, but orally administered anticoagulants depress levels of factors II, VII, IX, and X in the fetus). It is unclear whether mothers suffering from thromboembolic complications and taking warfarin should breast-feed their infants. The authors say no, but the only study cited showed that breast milk of such mothers had undetectable levels of anticoagulant. The discussion of possible mechanisms of intraventricular hemorrhage in the neonate is complete, but recommendations for therapy could be more detailed.

A relatively common clinical problem is neonatal isoimmune thrombocytopenia (ITP). In the "neonatal" chapter, cesarian section is recommended for subsequent pregnancies, whereas a more conservative approach is advocated in the "pregnancy" chapter. The reader could benefit from specific advice: How long should the neonate be treated with corticosteroids? Should the mother be given corticosteroids prior to delivery of her second baby if the first had neonatal ITP? What happens if transfused maternal platelets have a short time of survival? The possibility of subclinical maternal ITP must be suspected in this situation. Only the barest details of inherited hemorrhagic disorders are provided. The major screening tests are covered superficially, and references for some (eg, thromboelastogram, recalcification time, thrombotest, thrombin time, reptilase time, and clot stability test) are not provided. The uninitiated would have little appreciation for the strengths and weaknesses of each of the suggested laboratory tests. More tables and figures would add to the clarity of presentation, and some could be improved by dealing only with perinatal disorders rather than with abnormalities affecting older children.

A major problem facing neonatologists is the laboratory characterization and definition of DIC in the premature infant. In the authors' laboratory, the diagnosis of DIC is based on platelet count, PT, PTT, fibrogen degradation products, fibrinogen, and blood smear tests. If all are normal, DIC is not present. The problem arises when the results of some but not all of these studies are abnormal. A more detailed definition of DIC is needed and, again, data based on the authors' own experience would be extremely helpful. More details regarding the duration of therapy with heparin in DIC, and the best method for monitoring heparin effects are needed as well. The measurement of whole-blood clotting time in the neonate is fraught with technical problems and error, particularly if left in the hands of fatigued house officers at 3 AM.

The last chapter, on coagulation changes in preclampsia, eclampsia, and fetal growth retardation, provides some of the most interesting material in this book. Fibrin deposition and intimal lipid in uteroplacental arteries occur in preclampsia and are similar to findings in atheroma, atherosclerosis, and rejected renal transplants, suggesting a similar mechanism of pathogenesis. The results of a controlled study using low dosage heparin and a platelet antiaggregating agent (dipyridamole) in women at high risk for eclampsia and fetal growth retardation will be eagerly awaited. Such studies reflect the real objectives of collaborative clinical and laboratory investigation in perinatal centers. On that note, this new text should be useful to nurses, medical students, residents, and attending physicians working in university-affiliated perinatal units, and to generalists (obstetricians and pediatricians) in community hospitals who wish to brush up their knowledge of perinatal coagulation.

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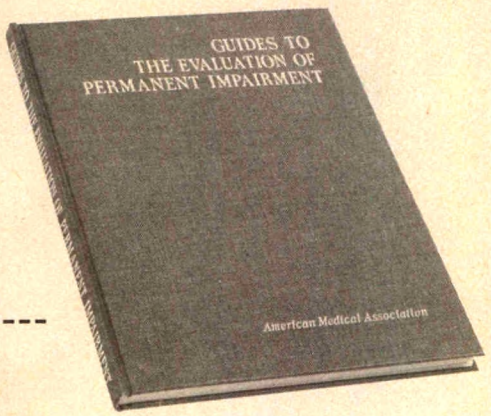

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National Council on Child Health,[1] Ritalin was described as among the most effective and best-documented agents for stimulant therapy in hyperkinetic children.

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Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

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Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

*Attention Deficit Disorders: new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

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TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

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References

1. Kugel RB, Scherz RG, Seidel HM, et al: Council on Child Health: Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4):560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al: Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30**:354-359.
3. MacKay MC, Beck L, Taylor R: Methylphenidate for adolescents with minimal brain dysfunction. *N Y State J Med* 1973 (Feb.); **73**:550-554.

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When/Where
Mon., Tues., Wed., April 21-23, 1980
The Marriott Hotel, Boston (Newton), MA

Subject Matter
Presentations will focus on erythrocyte disorders, with emphasis on: genetically and functionally abnormal hemoglobins, disorders of the erythrocyte membrane and cytoskeleton, susceptibility of erythrocytes to toxic agents (such as lead and mercury) and instrumental aspects of diagnosis.

State-of-the-art research findings and their clinical significance will be emphasized. Ample time will be allotted for discussion and questions.

Accreditation
Participants may receive accreditation from Tufts University School of Medicine (17 credit hours, Category I, A.M.A. Physician's Recognition Award).

How to Register
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Brief Summary

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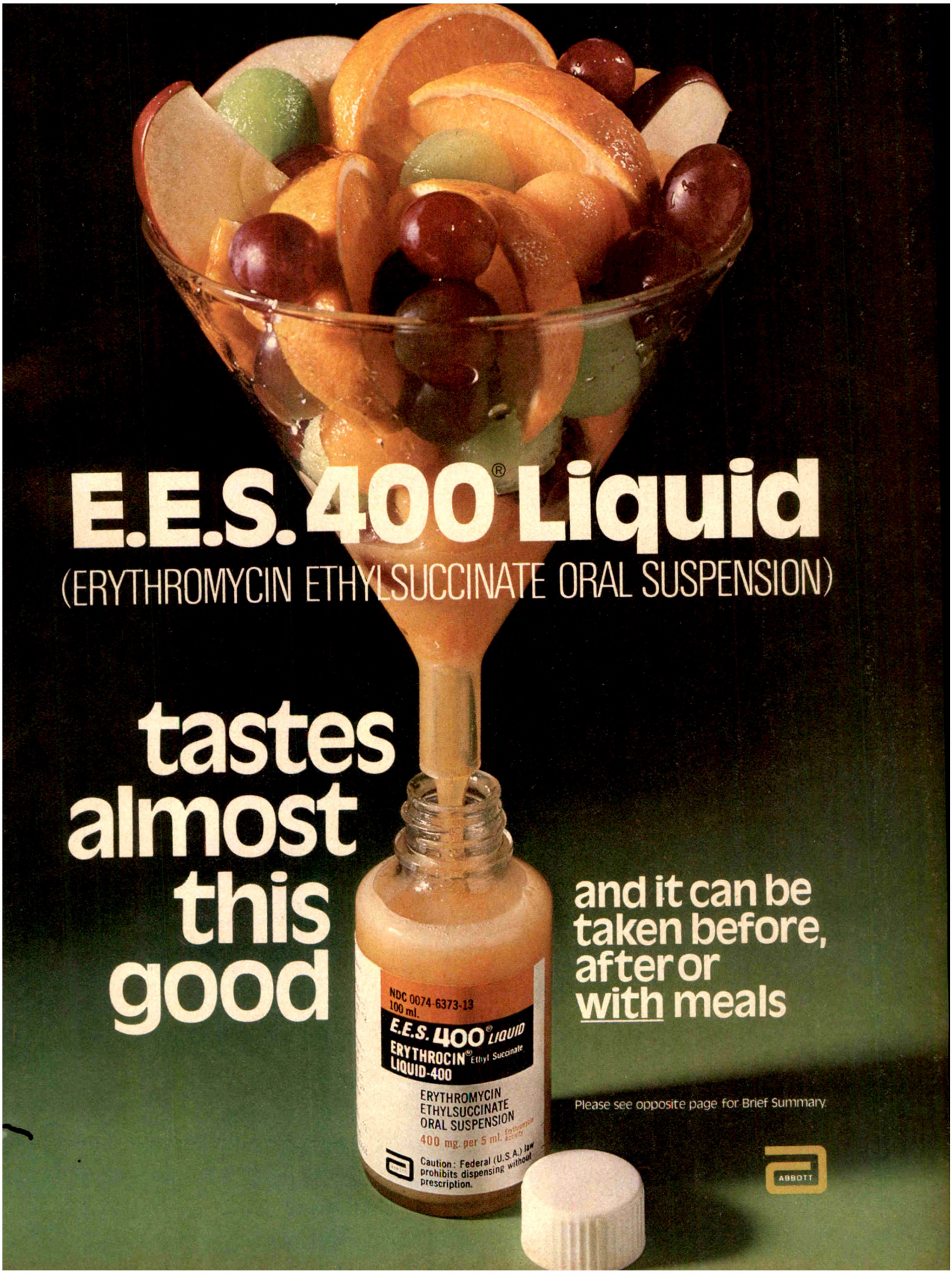
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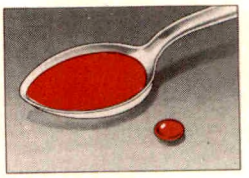

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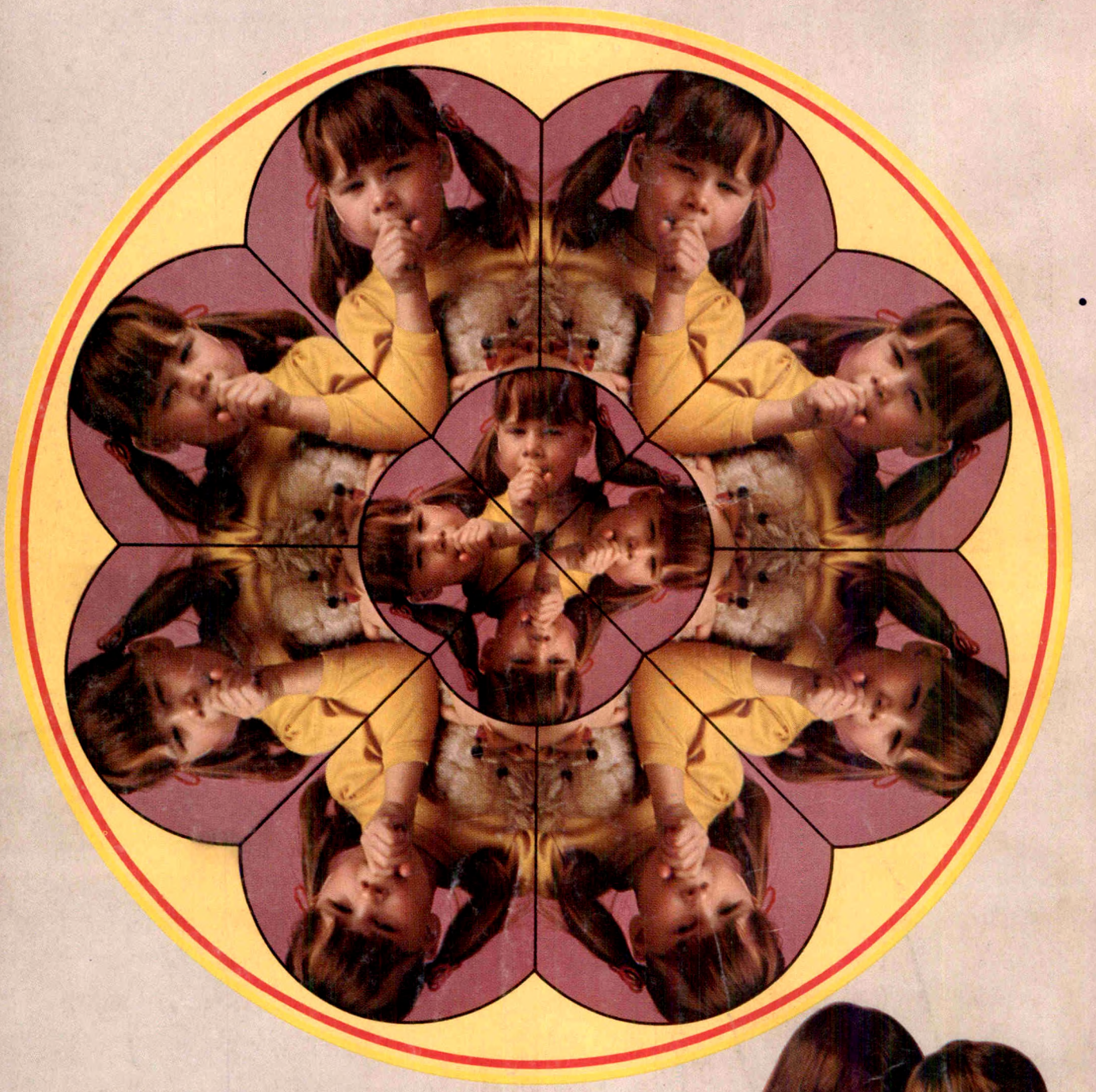

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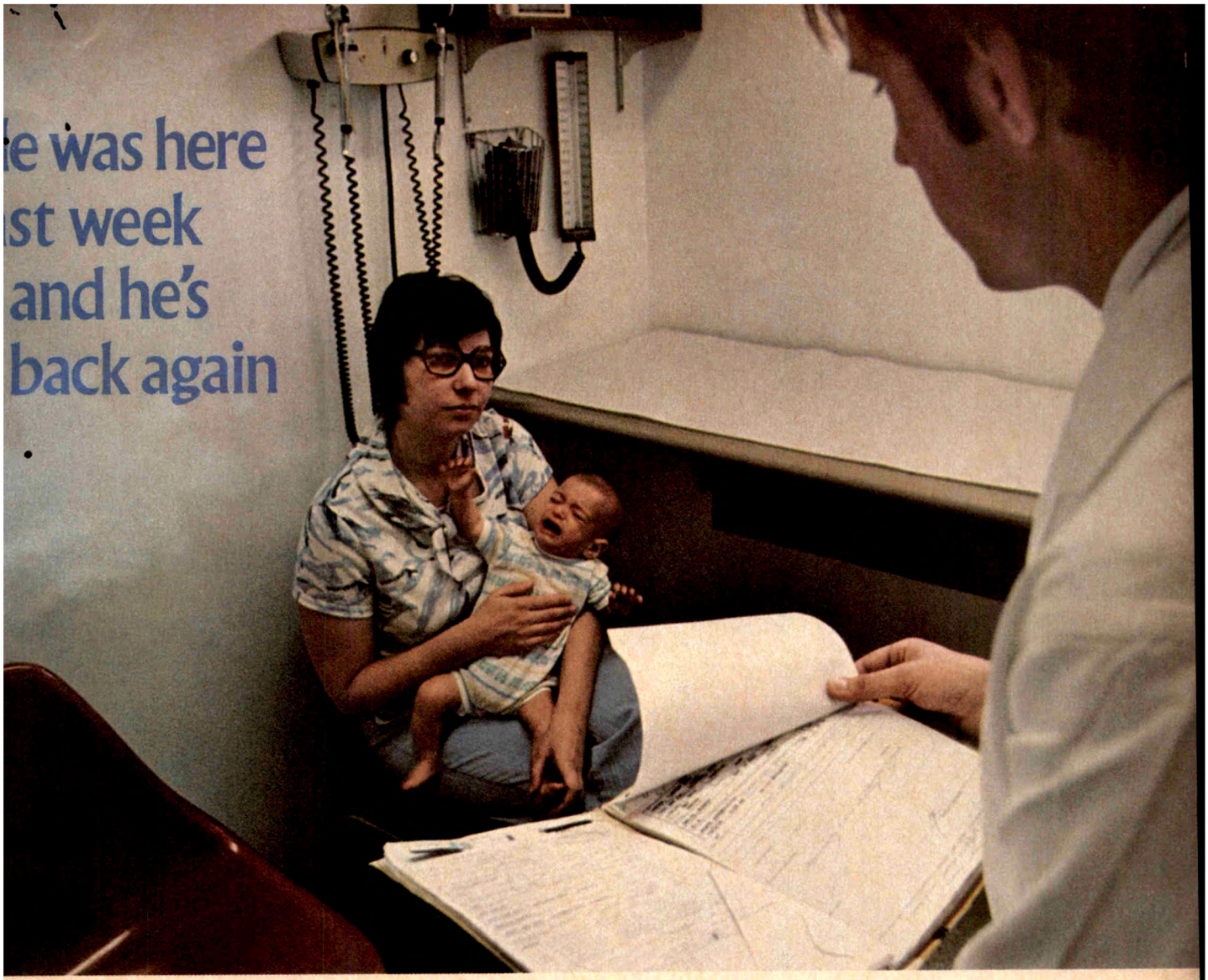

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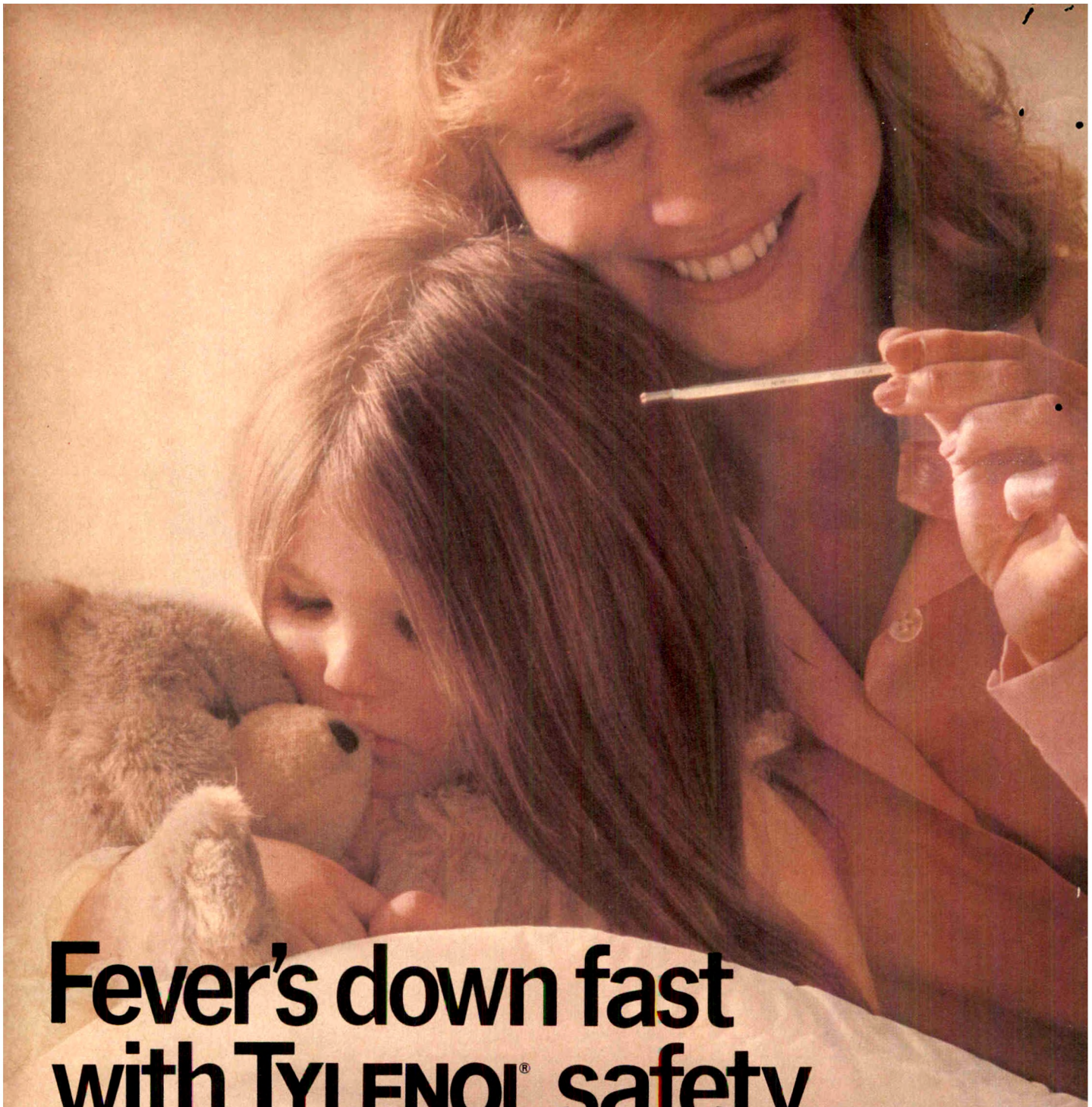

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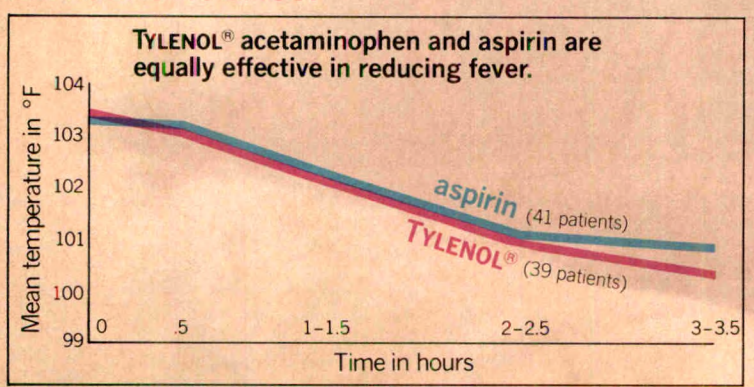

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ONE HUNDRED YEARS WELLCOME

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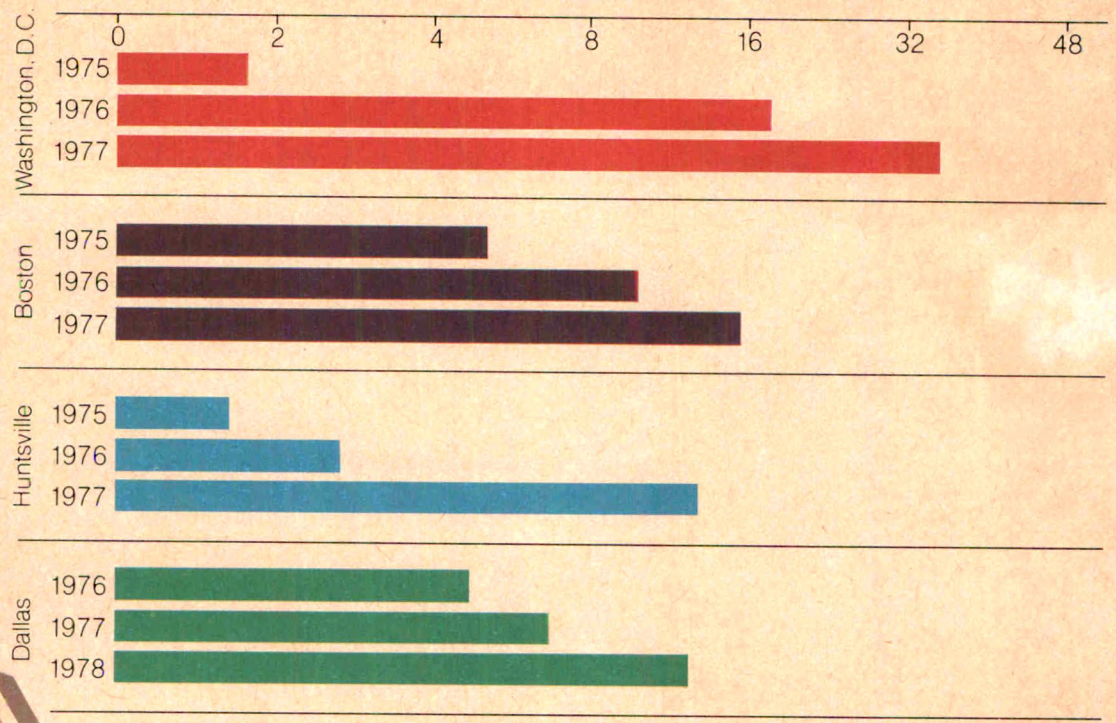
North Carolina 27709

Increasing resistance o



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor®(cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE)

Antibiotics, including Ceclor® (cefaclor, Lilly), should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it

Haemophilus influenzae in otitis media...

a valid concern

In many areas of the country, increasing numbers of *H. influenzae* show resistance to conventional antibiotic therapy.[1-3]

Ceclor is effective in the treatment of otitis media,† including that due to ampicillin-resistant strains of *H. influenzae*.[4-9]

Ceclor has been shown to be clinically and bacteriologically effective in treating otitis media due to susceptible organisms.[10]

Ceclor is available in two pleasant-tasting liquids.

Ceclor provides effective single-agent antibiotic therapy for otitis media.

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

† Due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes*.

125-mg/5-ml and 250-mg/5-ml oral suspensions

Ceclor®

cefaclor

should be recognized that a positive Coombs test may be due to the drug.

Ceclor ® (cefaclor, Lilly) should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below:

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count; predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0703790]

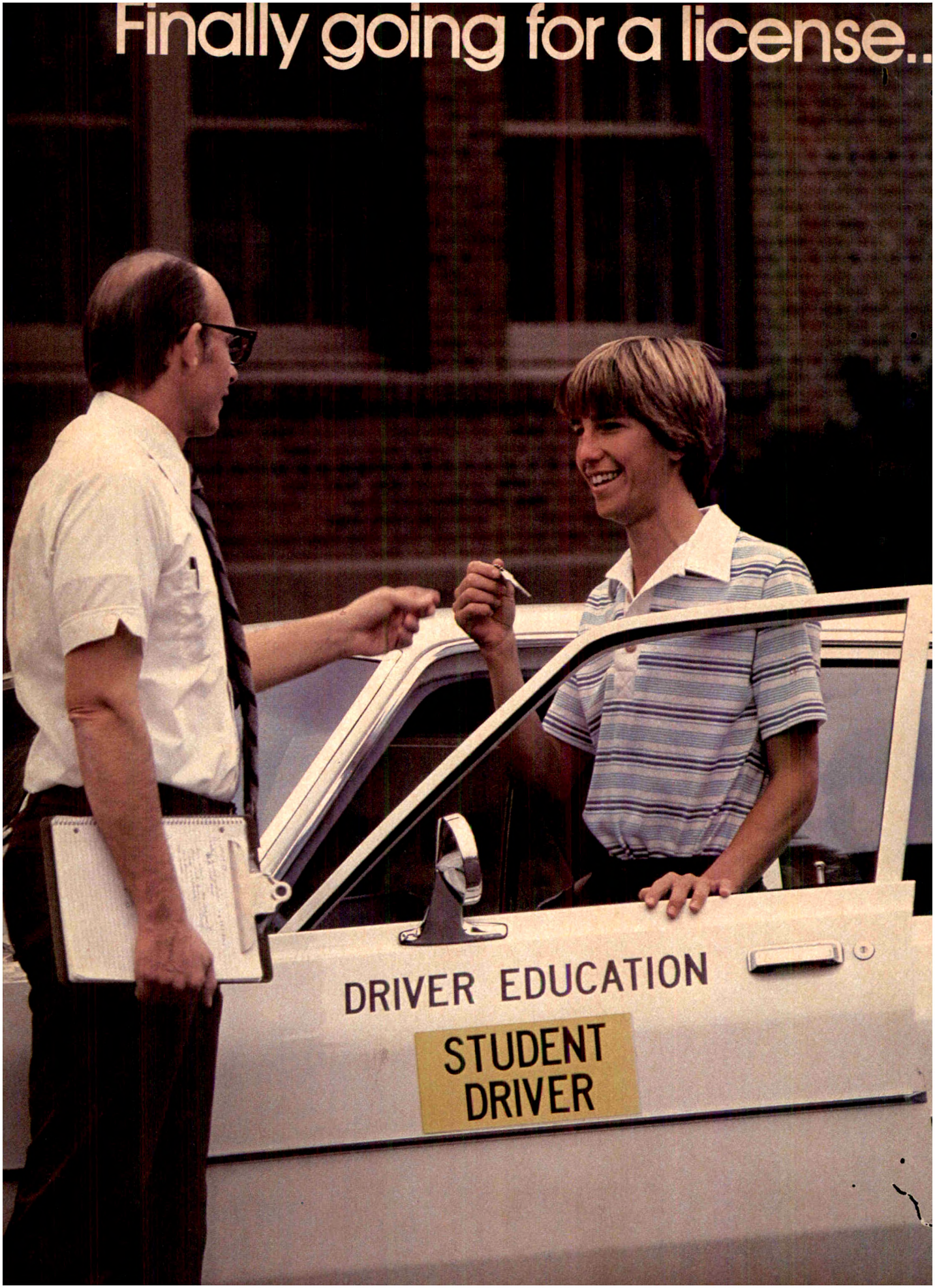
References

1. J. Pediatr., *92*:889, 1978.
2. J. Pediatr., *94*:983, 1979.
3. J.A.M.A., *239*:320, 1978.
4. Antimicrob. Agents Chemother., *11*:470, 1977.
5. Antimicrob. Agents Chemother., *13*:584, 1978.
6. Antimicrob. Agents Chemother., *12*:490, 1977.
7. Current Chemotherapy, *II*:880, 1978.
8. Antimicrob. Agents Chemother., *8*:91, 1979.
9. Antimicrob. Agents Chemother., *13*:861, 1978.
10. Data on file, Eli Lilly and Company.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Lilly

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630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DRIVER EDUCATION
STUDENT
DRIVER

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Valproic Acid

For your patients with mixed seizures including absence, or pure absence

More than just effective seizure control[1]

In 28 studies of patients with mixed grand mal and absence, 76% of all patients gained significant improvement; over one-third became seizure-free. In 60 studies involving pure absence, 86% of patients were improved; half became seizure-free.

Freedom from social stigmata is important too

With Depakene, social function is unimpeded by drug-induced hirsutism or gingival hyperplasia. Intellectual function may improve as more sedative drugs are reduced in dosage or withdrawn. Patients may be able to lead a more normal life with Depakene than was possible with their previous drug regimen.

A widely useful anticonvulsant

Depakene is indicated as sole or adjunctive therapy in both simple and complex absence seizures. It is also indicated for adjunctive treatment of patients with multiple seizure types which include absence. Clinical response has been especially noteworthy among patients with generalized tonic-clonic attacks, or with minor motor seizures (e.g., myoclonic movements, akinetic seizures), where combined with absence.

Offering your patients a chance for a better life

Sustained freedom from seizures can mean a drivers license, an active social schedule, involvement in athletic competition—a better life for your patient. Depakene has not been associated with hirsutism or gingival hyperplasia. Sedation has not been a frequent problem. The most common side effect with Depakene is G.I. upset, which usually responds to temporary dosage reduction. Serious side effects, including fatal hepatitis, have occurred.

1. Worldwide studies of Depakene experience (Data refer only to grand mal and/or absence seizures. Since each type was evaluated separately, some patients appear in both groups. Though most of these studies were uncontrolled and had widely differing protocols, their collective data clearly support efficacy of the drug).

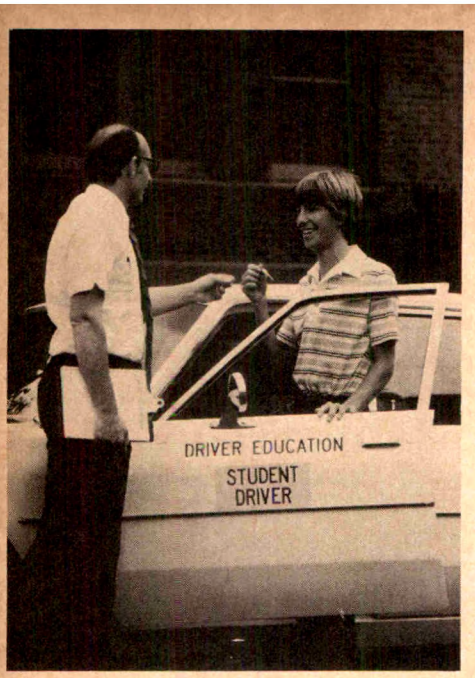
See overleaf for brief summary of prescribing information

Abbott Laboratories,
North Chicago, Illinois 60064

0013326R

Offering a chance for a better life
for your patients with mixed seizures including absence, or pure absence

Depakene®
Valproic Acid



Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

A BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported but do not appear dose related. (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increased dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

0013326

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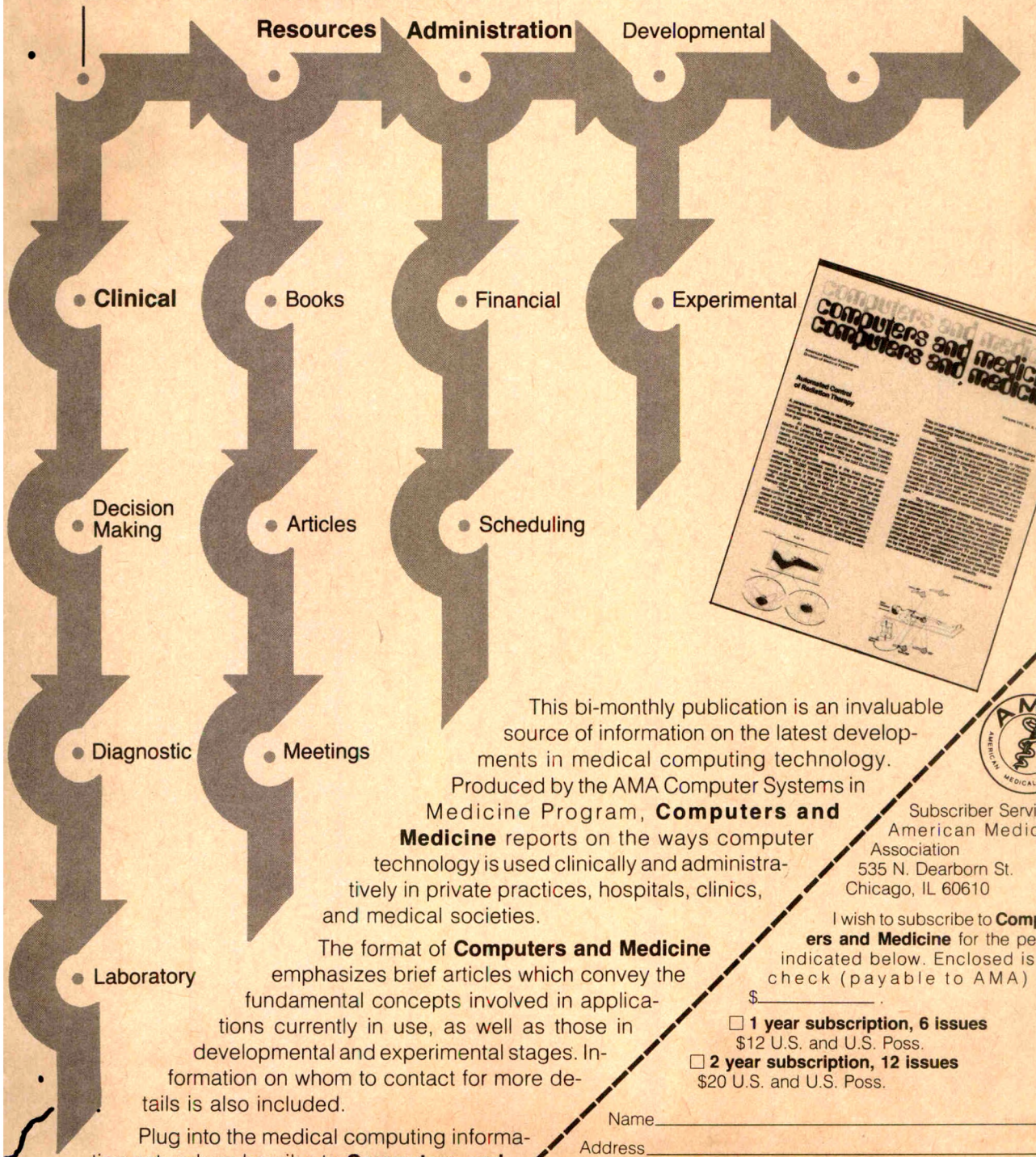

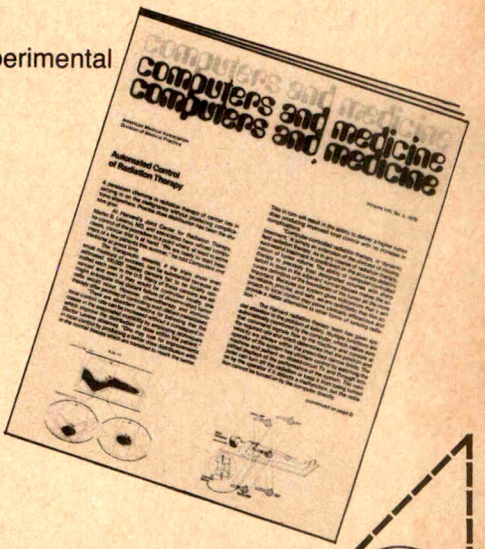

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NOW PETER

Attention Deficit Disorders* under control...
His natural abilities are coming through

Now Peter's enjoying more things at play as well as in school. He works better with his teacher and classmates... likes doing things with his dad... gets more natural pleasure out of family and friends.

Now that his concentration is improved, his natural abilities are coming through. He's functioning better. Under a well-integrated program of treatment for Attention Deficit Disorders (ADD), hyperactivity and impulsiveness are markedly reduced.

Ritalin (methylphenidate) can be a vital part of his regimen. With adjunctive use of Ritalin, many ADD children are better able to control hyperkinetic behavior —act in a more natural and appropriate manner.

A 20-year record of proven efficacy

Over the years, Ritalin has become an established choice for pharmacotherapy of ADD. In a report by the

BEHAVES MORE NATURALLY.

National Council on Child Health,[1] Ritalin was described as among the most effective and best-documented agents for stimulant therapy in hyperkinetic children.

Reduces hyperactivity, impulsive behavior

Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

Generally well tolerated

Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

***Attention Deficit Disorders:** new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

Ritalin . . . only when medication is indicated for Attention Deficit Disorders

Ritalin® C II

(methylphenidate)

as adjunctive therapy for ADD

Please turn page for brief prescribing information.

Ritalin® C II (methylphenidate)

Only when medication is indicated

Ritalin® hydrochloride (methylphenidate hydrochloride USP) C II

TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Tablets, 20 mg (peach, scored); bottles of 100 and 1000.

Tablets, 10 mg (pale green, scored); bottles of 100, 500, 1000 and Accu-Pak® blister units of 100.

Tablets, 5 mg (pale yellow); bottles of 100, 500 and 1000.

Dispense in tight, light-resistant container (USP).

665382 C80-14 (1/80)

Consult complete product literature before prescribing.

References

1. Kugel RB, Scherz RG, Seidel HM, et al. Council on Child Health: Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4):560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al. Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30**:354-359.
3. MacKay MC, Beck L, Taylor R. Methylphenidate for adolescents with minimal brain dysfunction. *NY State J Med* 1973 (Feb.); **73**:550-554.

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

175-01409-01

CIBA

Expressly for kids with colds that cough*

orange-pineapple flavored

Tuss-Ornade® cough/cold liquid

Each 5 ml. teaspoonful contains 5 mg. caramiphen edisylate; 2 mg. chlorpheniramine maleate; 15 mg. phenylpropanolamine hydrochloride; isopropamide iodide equivalent to 0.75 mg. of isopropamide; and alcohol, 7.5%.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Indications**

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Lacking in substantial evidence of effectiveness as a fixed combination: For relief from coughing, upper respiratory congestion and hypersecretion associated with the common cold, sinusitis, vasomotor rhinitis and allergic rhinitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any component; concurrent MAO inhibitor therapy; severe hypertension; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Do not use 'Tuss-Ornade' Liquid in children less than six months of age or under 15 lbs. in weight. Do not use 'Tuss-Ornade' *Spansule* capsules in children under 12 years of age.

Warnings: Warn vehicle or machine operators of possible drowsiness. Warn patients of possible additive effects of alcohol and other C.N.S. depressants.

Usage in Pregnancy: Use in pregnancy, nursing mothers and women who might bear children only when potential benefits have been weighed against possible hazards. An inhibitory effect on lactation may occur.

Effect on PBI Determination and I^{131} Uptake: The iodine in isopropamide iodide may alter PBI test results and will suppress I^{131} uptake; use thyroid tests unaffected by exogenous iodides.

Precautions: Use with caution in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.

Adverse Reactions: Drowsiness; excessive dryness of nose, throat or mouth; nervousness, insomnia; nausea, vomiting, diarrhea; rash; dizziness; weakness; tightness of chest; angina pain; abdominal pain; irritability; palpitation; headache; incoordination; tremor; difficulty in urination; thrombocytopenia, leukopenia; convulsions; hypertension, hypotension; anorexia; constipation; visual disturbances; iodine toxicity (acne, parotitis); dysuria; epigastric distress.

Supplied: 'Tuss-Ornade' Liquid: An orange-pineapple flavored liquid in 16 fl. oz. bottles. For patients 12 years or older, 'Tuss-Ornade' *Spansule* capsules (each capsule contains 20 mg. caramiphen edisylate; 8 mg. chlorpheniramine maleate; 50 mg. phenylpropanolamine HCl; and isopropamide iodide equivalent to 2.5 mg. of isopropamide), in bottles of 50 and 500 capsules.

SK&F a SmithKline company

Smith Kline & French Laboratories
Div. of SmithKline Corp., Phila., Pa.

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All the elements of a manuscript should be submitted in **triplicate, double-spaced throughout.** Use heavy-duty white bond paper, 22 × 28-cm, and 4-cm margins. The style of writing should conform to proper English usage and syntax. All measurements are to be in metric units, temperatures in Centigrade.

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Brief accounts of interesting observations and clinical situations. Limited to 800 words plus one table or illustration; abstract unnecessary. Submit in triplicate, double-spaced. Copyright assignment required.

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1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 131:295-296, 1977.
2. Koller LR: *Ultraviolet Radiation*, ed 2. New York, John Wiley & Sons Inc, 1965, pp 141-160.
3. Daughaday WH: The adenohypophysis, in Williams RH (ed): *Textbook of Endocrinology*, ed 5. Philadelphia, WB Saunders Co, 1974, pp 31-79.

Do not include unpublished data, personal communications, or manuscripts "in preparation" or "submitted" in the list of references. Such material, if essential, may be incorporated in the body of the article.

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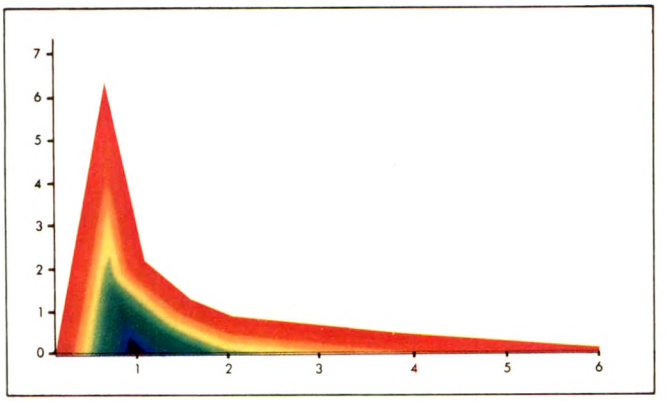
Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 22 × 28-cm paper. If a table must be continued, use a second sheet and repeat all heads. Each table must have a title.

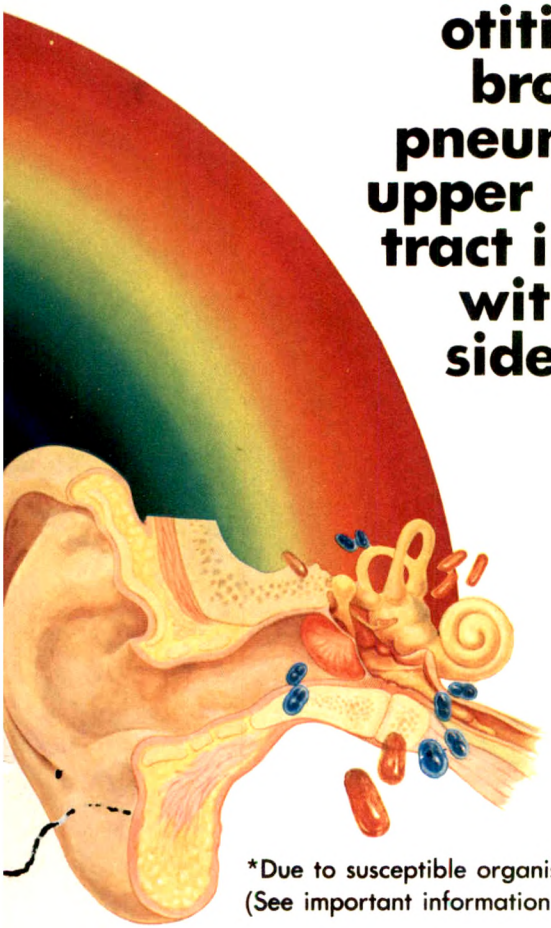
more than just spectrum

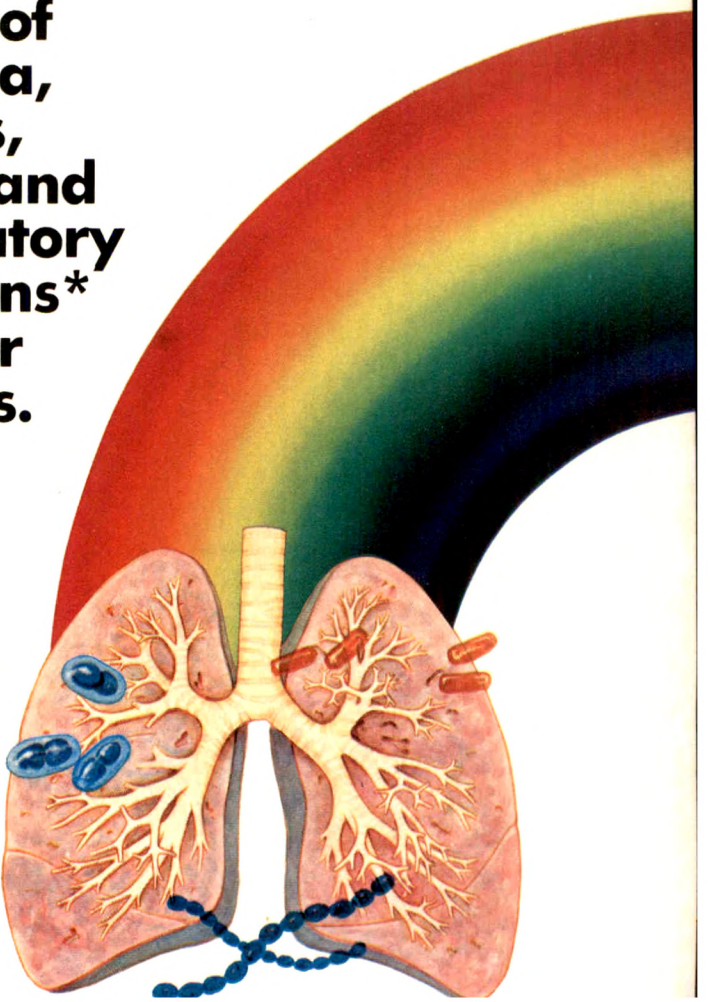


New CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Efficacy proven in the treatment of otitis media, bronchitis, pneumonia and upper respiratory tract infections* with fewer side effects.





*Due to susceptible organisms
(See important information on last page.)

N[illegible]®

(cyclacillin) Tablets/ Suspension

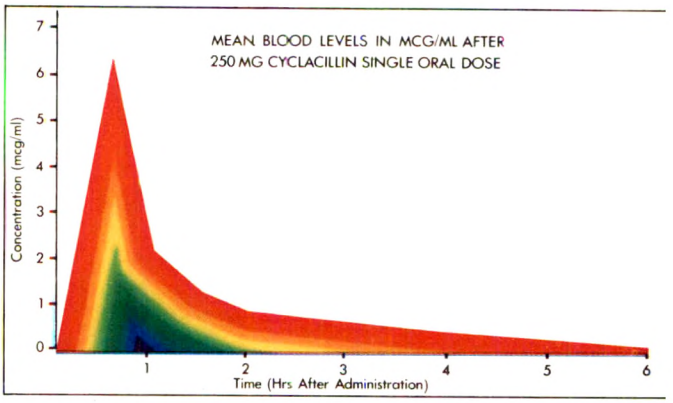
efficacy with fewer sid[illegible] ampicillin confirmed i[illegible] studies of 2,58[illegible]

Rapid, virtually complete absorption from GI tract

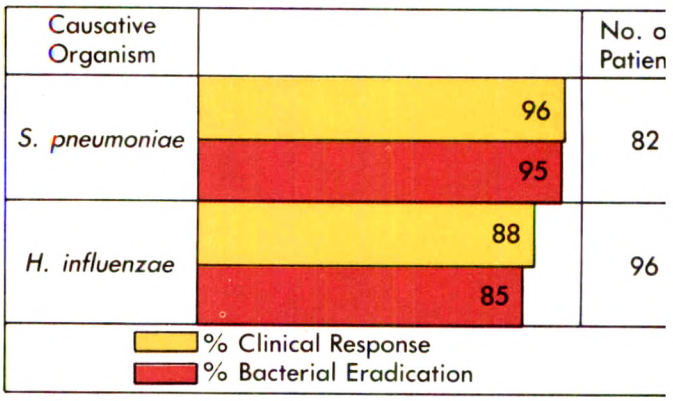
Rapid onset of action—mean peak serum levels within 30 minutes

Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)

Rapidly excreted unchanged in the urine—1½ times faster than ampicillin



Clinical efficacy of CYCLAPEN® in otitis media†



more than just spectru[illegible] in otitis media

*Includes all patients treated. 2,415 evaluated for safety; 1,819 evaluated for efficacy.

†Due to susceptible organisms.

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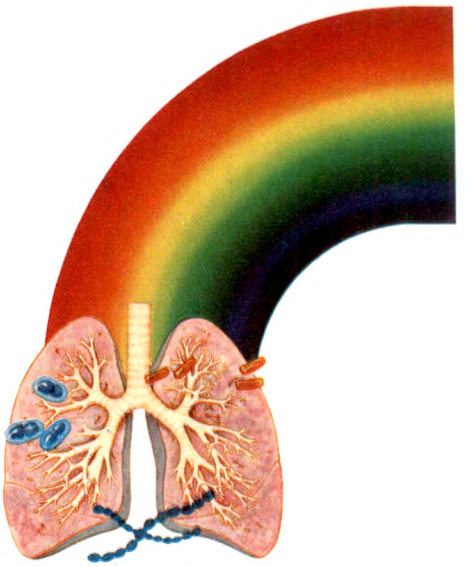
ffects than louble-blind patients*



wer side effects with CYCLAPEN® in uble-blind studies to date[1,2]

Total number of drug-related side effects in all patients	
CYCLAPEN®	128 of 1,286 (10%) of patients
ampicillin	202 of 1,129 (18%) of patients
Difference statistically significant (P <0.001)	

In bronchitis, pneumonia and upper respiratory tract infections†

High cure rate with CYCLAPEN®		
Causative Organism	Bronchitis/Pneumonia†	No. of Patients
S. pneumoniae	100 / 95	73
Chronic Bronchitis† (acute exacerbation)		
H. influenzae	92 — Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*	12
Streptococcal Sore Throat†		
Group A beta-hemolytic Streptococcus	100 / 86	44
% Clinical Response % Bacterial Eradication		

(CLAPEN® (cyclacillin)
fective for otitis media† in children

Excellent clinical results in eliminating the two most common causative organisms in otitis media

Significantly lower incidence of diarrhea and skin rash in children treated with CYCLAPEN® Suspension

	diarrhea	rash
CYCLAPEN	9.1%	2.1%
ampicillin	19.2%	5.8%
	P < 0.001	P < 0.03

more than just spectrum CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Gold JA, Hegarty CP, Deitch MW, Walker BR: Double-blind clinical trials of oral cyclacillin and ampicillin, *Antimicrob Ag Chemother* 15:55-58 (Jan.) 1979.

Data on file, Wyeth Laboratories.

ee important information on next page.)

Wyeth Laboratories
Philadelphia, Pa. 19101

New from Wyeth Laboratories

CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Usual children's dosage: 50 to 100 mg/kg/day in equally space doses, depending on severity.

more than just spectrum in otitis media, bronchitis, pneumonia, and upper respiratory tract infections*

- Rapid, virtually complete absorption from GI tract
- Rapid onset of action—mean peak serum levels within 30 minutes
- Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)
- Rapidly excreted unchanged in the urine—1½ times faster than ampicillin
- Significantly fewer episodes of diarrhea and skin rash than reported with ampicillin in studies to date
- Excellent clinical response and outstanding bacterial eradication documented in double-blind studies involving 2,581 patients
- New CYCLAPEN® Suspension—great-tasting raspberry punch flavor

*Due to susceptible organisms.

How Supplied

CYCLAPEN® (cyclacillin) tablets:
250 mg scored tablets
500 mg scored tablets

Indications

Cyclapen® (cyclacillin) has less in vitro activity than other drugs in the ampicillin class of antibiotics and its use should be confined to the indications listed below.

Cyclapen® is indicated for the treatment of the following infections:

RESPIRATORY TRACT

Tonsillitis and pharyngitis caused by Group A beta-hemolytic streptococci

Bronchitis and pneumonia caused by *S. pneumoniae* (formerly *D. pneumoniae*)

Otitis Media caused by *S. pneumoniae* (formerly *D. pneumoniae*) and *H. influenzae*

Acute exacerbation of chronic bronchitis caused by *H. influenzae**

*Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*.

SKIN AND SKIN STRUCTURES (integumentary) infections caused by Group A beta-hemolytic streptococci and staphylococci, non-penicillinase producers.

URINARY TRACT INFECTIONS caused by *E. coli* and *P. mirabilis*. (This drug should not be used in any infections caused by *E. coli* and *P. mirabilis* other than urinary tract infections.)

NOTE: Cultures and susceptibility tests should be performed initially and during treatment to monitor the effectiveness of therapy and the susceptibility of bacteria. Therapy may be instituted prior to the results of sensitivity testing.

Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to penicillins.

Warnings

CYCLACILLIN SHOULD ONLY BE PRESCRIBED FOR THE INDICATIONS LISTED IN THIS INSERT.

CYCLACILLIN HAS LESS *IN VITRO* ACTIVITY THAN OTHER DRUGS OF THE AMPICILLIN CLASS ANTIBIOTICS. HOWEVER, CLINICAL TRIALS HAVE DEMONSTRATED THAT IT IS EFFICACIOUS FOR THE RECOMMENDED INDICATIONS.

SERIOUS AND OCCASIONAL FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING PENICILLIN.

ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL ADMINISTRATION, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE ARE REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY REACTIONS WHO EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH A CEPHALOSPORIN. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE ABOUT PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY SHOULD BE INITIATED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

PREGNANCY: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to ten times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cyclacillin is administered to a nursing woman.

Adverse Reactions

The oral administration of cyclacillin is generally well tolerated.

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated

CYCLAPEN® (cyclacillin) fc
oral suspension
125 mg per 5 ml:
100 ml and 200 ml bottles
250 mg per 5 ml:
100 ml and 200 ml bottles

hypersensitivity to **penicillins** or in those with a history of allergy, ast fever, or urticaria.

The following adverse reactions have been reported with the use of c diarrhea (in approximately 1 out of 20 patients treated), nausea and (in approximately 1 in 50), and skin rash (in approxrmately 1 in 60) instances of headache, dizziness, abdominal pain, vaginitis, and urtic been reported. (See WARNINGS)

Other less frequent adverse reactions which may occur and that h reported during therapy with other penicillins are: anemia, thromboc thrombocytopenic purpura, leukopenia, neutropenia and eosinophili reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been r

Dosage and Administration

INFECTION*	ADULTS	CHILDREN
		Dosage should n in a dose higher t for adults.
Respiratory Tract		
Tonsillitis & Pharyngitis**	250 mg q.i.d. in equally spaced doses	body weight <2(lbs) 125 mg q equally spaced d body weight >2(lbs) 250 mg q equally spaced d
Bronchitis and Pneumonia		
Mild or Moderate Infections	250 mg q.i.d. in equally spaced doses	50 mg/kg/day (equally spaced d
Chronic Infections	500 mg q.i.d. in equally spaced doses	100 mg/kg/day equally spaced d
Otitis Media	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/k equally spaced d pending on severi
Skin & Skin Structures	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/k equally spaced d pending on severi
Urinary Tract	500 mg q.i.d. in equally spaced doses	100 mg/kg/day in spaced doses.

*As with antibiotic therapy generally, treatment should be continue minimum of 48 to 72 hours after the patient becomes asymptomatic evidence of bacterial eradication has been obtained.

**In infections caused by Group A beta-hemolytic streptococci, a mini 10 days of treatment is recommended to guard against the risk of rh fever or glomerulonephritis.

In the treatment of chronic urinary tract infection, frequent bacteriolc clinical appraisal is necessary during therapy and may be required for months afterwards.

Persistent infection may require treatment for several weeks.

Cyclacillin is not indicated in children under 2 months of age.

Patients with Renal Failure

Based on a dosage of 500 mg q.i.d., the following adjustment in interval is recommended:

Patients with a creatinine clearance of >50 ml/min need age interval adjustment.

Patients with a creatinine clearance of 30-50 ml/min should rec doses every 12 hours.

Patients with a creatinine clearance of between 15-30 ml/mir receive full doses every 18 hours.

Patients with a creatinine clearance of between 10-15 ml/mir receive full doses every 24 hours.

In patients with a creatinine clearance of ≤10 ml/r serum creatinine values of ≥ 10 mg %, serum cyclacillin levels are mended to determine both subsequent dosage and frequency.

Wyeth Laboratories
Philadelphia, Pa. 19101

The Many Advantages of Direct Microfocus Roentgenographic Magnification in Pediatric Radiology

A Portable X-ray Machine With a Uniquely Different X-ray Tube

Direct radiographic magnification as a means of complementing diagnostic imaging is not a new concept.[1] The technique has been used widely, but never applied generally because a "bigger" image was not necessarily a "better" image. The physics of direct roentgenographic imaging is a complex marriage of x-ray beam geometry and the physicochemistry of photon absorption within a cassette.

Until the time of development of the Radiological Sciences Inc (RSI) x-ray tube, virtually all medical x-ray tubes depended on a hot tungsten filament as the initial source of electrons for the generation of x-ray photons (ie, since 1913, when Coolidge[2] introduced the first filament x-ray tube). Detail in magnification is adversely affected by imperfections in the beam source. The standard filament x-ray tubes usually produce two point sources and a trailing edge of radiation off their axes. The resultant images are blurred, and this blurring is amplified by magnification. Therefore, the more precise the point source, the sharper the projected image.

The RSI tube uses a smooth tungsten block as an electron source. Five electron-focusing lenses in the tube produce a focal spot of about 90 μ. Although there is a small difference between microfocus (90 μ) and conventional fractional focal spots (100 μ), it is the single sharp point source that accounts for the improvement. The advent of the microfocus tube opened the way for the second essential step.

It has been shown repeatedly that the very high-speed, intensifying screen-x-ray film recording systems provide excellent roentgenographic detail when used for direct magnification.[3] Very high-speed (rare earth) systems may not provide satisfactory detail for some (nonmagnified) roentgenographic examinations.

However, the appropriate implementation of a microfocus x-ray source with a cassette containing rare earth recording material results in enlargement of the anatomic part, with better detail than is available by the techniques of standard roentgenography.

Clinical application of this new modality has not reached its full potential; however, our experience at the Cardinal Glennon Memorial Hospital for Children, St Louis, points to future applications.

FUTURE USES

Bone

Trauma.—Threefold magnification opens up a new area of early and confirmed diagnosis. For example, minimal periosteal reaction is detectable much more easily. Minute chip fractures in infant bone may not be detectable by any other means, although minute fractures can occasionally be detected by techniques such as "nonscreen" and xeroradiographs. The radiation dose is greater by a factor of about four for xeroradiography.

Scaphoid Injury.—Often, suspicion of fracture of the scaphoid requires multiple views to resolve the question. A single direct magnification projection may solve the problem. For most of us, confirming the "normal" may be just as important as showing the abnormal.

Abused Children.—Abused babies may sustain minute metaphyseal avulsion fractures as the result of violent shaking, jerking, and twisting. These findings might allow us to move through the complexities of evaluating the "suspected" battered child with greater confidence and in a much shorter time. The demonstration of such fractures are admissible as evidence in court.

Radionuclide scintigraphy may identify areas of hyperemia within a few hours after trauma. In most instances, the region already is under suspicion, so that what is needed is a definitive morphological demonstration. Magnification may be the only low-radiation technique that can detect minute fractures.

Inflammation.—The early use of antibiotics has changed the natural evolution of radiographic bone change in osteomyelitis. The earliest roentgenographic change is deep, soft-tissue edema. The use of xeroradiographic or "nonscreen" techniques is discouraged

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because of the greater amount of radiation required. A single view, threefold magnification provides excellent soft-tissue visualization because of the contrast enhancement that is part of all such roentgenographs, and it also establishes a baseline for sequential comparisons. Minimal bone destruction or periosteal reaction may be better documented by magnification than by other techniques. Radionuclide scintigraphy may identify areas of increased uptake, but do not specify bone destruction.

Tumor.—We find increasingly that discrimination can be made between benign and malignant bone tumors. Early malignant bone change particularly lends itself to more precise evaluation. Improved resolution in bone tumor cases has encouraged operative confirmation without intervening tomographic and vascular studies (Fig 1 through 3).

Arthritis.—Used as a baseline roentgenogram, fourfold magnification of a finger is an excellent means for early identification of arthritic change and for detection of its subtle differential characteristics.

Middle Ear Disease

Structures in the base of the skull and, especially, the middle ear can be magnified with ease, allowing for visualization of the tympanum, malleus, and incus. We use the technique when indicated to complement a petromastoid examination.

Temporomandibular (TM) Joint

Conventional roentgenography of the TM joint may be an enigma to many radiologists and maxillofacial surgeons. A threefold magnification of a lateral TM joint projection may show precise cortical detail of both subchondral surfaces. Recent work by Murphy and associates[4] has greatly enhanced the usefulness of techniques for the study of TM joint abnormalities by having introduced a new positioning device.

Chest

Taking advantage of the high-speed image recording, microfocus direct roentgenographic magnification of the chest becomes a practical reality

Fig 1.—Skull roentgenogram of 10-year-old boy who had soft, fluctuant mass in scalp, with area of bone destruction near vertex (arrow).

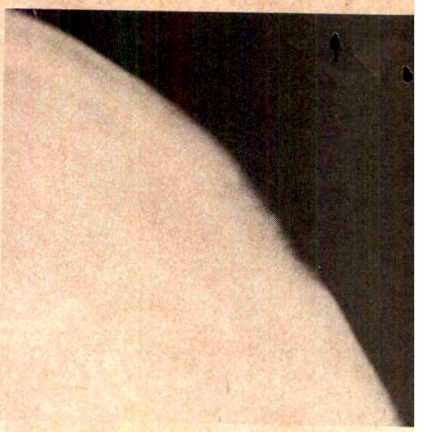
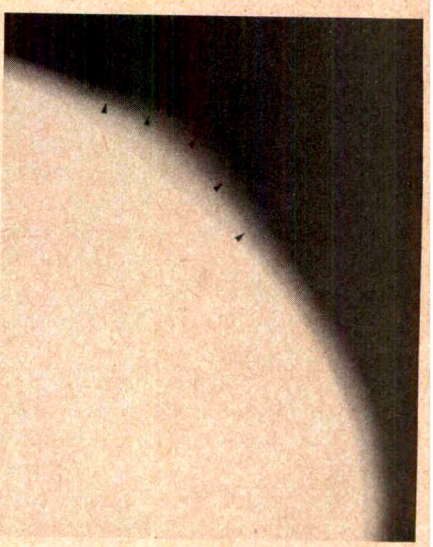


Fig 2.—Oblique threefold magnification roentgenogram of that same portion of calvaria, clearly showing destruction of outer table and intact inner table. Destruction is very irregular; some invasion into diploic space is seen.

Fig 3.—Same region as shown on Fig 2, except that threefold magnification roentgenogram was made for soft tissue. Contrast enhancement afforded by magnification shows tissue planes, outline of mass in deep soft tissues (arrows), and no evidence of inflammation (edema). On basis of fact that bone is destroyed and invaded, and fact that there is no evidence of edema, diagnosis of tumor was made. Biopsy specimen confirmed osteosarcoma.



in the neonate. We are convinced that many pediatric radiologists and some neonatologists have little need for roentgenographic enhancement in the daily pursuit of their specialty. For them, magnification of the chest of a small premature infant may be unnecessary. However, for the general radiologist or the pediatrician who ponders over the changes at the base of the lung in a tiny baby, roentgenographic enlargement can be a godsend by providing improved image detail as well as roentgenographic enlargement. The subtle changes of hyaline membrane disease, of congenital heart disease, and of pulmonary interstitial emphysema are more readily appreciated with this technique.

PRACTICAL APPLICATION

First, radiologic technologists are able to manipulate routine magnification techniques with the same ease and facility as they do with standard contact radiography. Second, bone detail is of such high quality that the "additional" or "second" view in doubtful cases could be a magnified one. Depending on the initial imaging system used, the "image" may show improved bone detail. Third, the magnified chest roentgenograph defines the minutiae of pathologic change, rendering the pattern more recognizable. It is only the most experienced pediatric radiologist who does not need this technique. Finally, our initial experience with microfocus magnification applications in vascular angiography and in image amplification, spot "film" roentgenography indicates that there are very definite advantages to the radiologist. In fact, it would seem that until the advent of the RSI tube, magnification of small vessels was impractical because the

bigger image was not necessarily a better image, and because it was also more blurred.

The use of extremely high-speed rare earth screen/film recording systems is practical and effective. In our experience, the Trimax 12 (3M Company) intensifying screens, combined with X-M or X-D orthochromatic film has proved to be the fastest available system that will record in satisfactory detail. The greatest single advantage is the increased margin of confidence it provides to the daily challenge of diagnosis.

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References

1. Sandor T, Adams DF, Herman PG, et al: The potential of magnification angiography. *Am J Roentgenol* 120:916-921, 1974.
2. Coolidge WD: A powerful roentgen ray tube with a pure electron discharge. *Am J Roentgenol* 1:115-124, 1914.
3. Doi K, Imhoff H: Noise reduction by radiographic magnification. *Radiology* 122:479-487, 1977.
4. Murphy WA, Adams RJ, Gilula LA: Magnification radiology of the temporomandibular joint. Presented at the Annual Scientific Meeting of the Radiological Society of North America, Chicago, Nov 30, 1978.

Condoms for Sexually Active Adolescents

To the individual physician, public health statistics sometimes have a way of seeming so awesome as to appear abstract and remote. In a way, the grim numbers of teenage pregnancies and sexually transmitted diseases (STDs) are reminiscent of the casualty reports from the Viet Nam War. One recognizes that something large and awful is taking place, but the problem is perceived to be so massive that any control measures attempted would have as much influence as spitting in the ocean.

Though the public at large may not appreciate the full dimensions of the teenage pregnancy problem, physicians, and especially pediatricians, cannot hide behind a shield of ignorance. Most of us have daily dealings with the offspring of children who are too young biologically and emotionally to be parents. The most obvious example is the inordinate number of low-birth-weight infants that are born to teenage mothers. Imagine the impact on the "business" of neonatal intensive care units if even a small dent were made in teenage pregnancy rates! We would also see a decrease in the number of cases of mental retardation, cerebral palsy, sudden infant death syndrome, child abuse, and a host of other maladies related to prematurity.

In terms of overall morbidity, the greatest amount of long-term damage from teenage pregnancy comes from the frequent lack of a nurturing substrate required to adequately sustain the minds and souls of children. Children born into capable and loving families have enough obstacles to overcome on the way to productive adulthood. Why start life with two strikes?

Whatever one thinks about the rights or wrongs of premarital sexual activity, "it" is in fact occurring—a lot! To wish the situation away by moral pronouncements is like taking a stand for a flat earth.

CASUALTY FIGURES

The "casualty figures" bear recounting. In 1975, about 1.1 million pregnancies occurred in the United States to teenagers aged 15 to 19 years, which works out to one of ten teenage girls. More than half these pregnancies (55%) resulted in live births, 31% terminated in abortions, 14% resulted in fetal loss. In 1966, 3 million adolescents were believed to be sexually active; by 1975, the figure increased to 4.5 million—a 50% increase during a decade. In 1975, it was estimated that 55% of all unmarried 19-year-olds had engaged in intercourse.[1] There is every reason to believe that these upward trends in teenage sexual activity are continuing.

What about contraceptive practices? Kantner and Zelnik,[2] in their 1973 study of a national sample of never-married girls aged 15 to 19 years, found that about 20% in all age groups had always tried to protect themselves against pregnancy and that 53% of all the girls studied failed to use any contraception the last time they had had intercourse. Seventy-one percent of the youngest girls used no contraceptive.

The most commonly used contraceptives among all age groups are the pill and the intrauterine device (IUD). They are certainly effective in preventing conception, and they produce relatively few complications in the mature woman with a consistent sexual partner. There are important drawbacks, however, in advocating the use of these agents in young teenagers. One is the necessity to visit a medical facility for a prescription or insertion, which may deter a sizeable number of youths. Ryde-Bloomquist[3] says:

> Older teenagers, well motivated to using contraceptives, seem to accept the pill well, but younger teenagers have difficulties in following the pill prescription and may forget to take them as their habits often tend to be disorganized. The same side effects, eg, weight gain, nausea and headaches, have been noticed among teenagers as among adult women. Many teenagers are frightened by these symptoms and discontinue using the pill, often abruptly.

The IUDs also present problems for many nulliparas. The expulsion and/or removal rate for pain, bleeding, and infection is consistently greater among teenagers than among those 20 years of age or older.[4]

The diaphragm with a spermicidal preparation is a safe and effective contraceptive method that is enjoying a comeback as the complications of the pill and IUD become more publicized. Unfortunately, this approach requires a degree of sophistication and planning that adolescents usually lack.

SEXUALLY TRANSMITTED DISEASES

An ominous development that is not sufficiently appreciated in the pediatric community is the widening spectrum and severity of STDs. Our current sexual "freedom" is a direct result of both improved methods of contraception and antibiotics to treat syphilis and gonorrhea. The potential consequences of indiscriminate sexual behavior were made clear to youngsters growing up prior to World War II. Undoubtedly, faced with the graphic specter of lifelong pain, disability, and sterility, many chose celibacy.

The availability of penicillin put an end to the stern admonitions of scoutmasters, top sergeants, fathers, and physicians. However, the power of the "magic bullet" is starting to weaken.

The Communicable Disease Center, Atlanta, reported that in 1977, there were 9,556 children between the ages of 10 and 14 years, and 252,473 teenagers from 15 to 19 years old who were *reported* to be infected with gonorrhea.[5] In the last decade, effective treatment of gonorrhea required much more penicillin than previously: 4.8 million units of penicillin G procaine intramuscularly along with a 1-g dose of oral probenecid. In addition, there is the emergence of penicillinase-producing *Neisseria gonorrhoeae*. Few teenagers are aware that about 15% of infected female subjects get some kind of inflammatory disease such as salpingitis, endometritis, or peritonitis, leading to infertility.

Although such organisms as *Trichomonas vaginalis*, *Haemophilus vaginalis*, and pediculosis pubis are not frequent adolescent clinic problems, two STD "newcomers," *Chlamydia trachomatis*, and herpes simplex virus (HSV) have emerged as formidable public health problems. Nongonococcal urethritis is now two to three times more common in the United States than *N gonorrhoeae* infection. *Chlamydia trachomatis* has been identified as the etiologic agent in 40% to 50% of these cases.[6] In addition, recent studies documented *C trachomatis* as an important pathogen in mucopurulent cervicitis and salpingitis and as a common cause of conjunctivitis and pneumonitis in infants. Unfortunately, diagnostic services to detect this important and treatable pathogen remain few and far between.

Similar problems exist with genital HSV infections. This disease with its weeping, painful, itchy, and crusty lesions and frequent recurrences is just plain messy, a fact that might have more impact on a today-oriented adolescent than the more dangerous, yet remote, prospect of neonatal herpes infection. The incidence of genital HSV infection is uncertain, but in the STD clinic at the Harborview Medical Center in Seattle, one case of genital HSV infection is diagnosed for every 2.2 cases of *N gonorrhoeae* infection.[7] This would extrapolate to about 300,000 clinical infections per year in the United States.

Neonatal herpes infection may occur in as many as one in 3,500 deliveries. More than half the cases of neonatal herpes infection occur in babies born to young primigravidas. And at least half of the infants with neonatal herpes infection either die or have permanent neurologic sequelae.[8] Can there be any better justification for pediatric involvement in attempts to control STDs?

In recommending a contraceptive, it should be borne in mind that oral contraceptives actually enhance the probability of a woman acquiring gonorrhea from an infected male partner.[9] The users of IUDs also have a five to seven times increased risk of getting both gonococcal and nongonococcal salpingitis.[10] Thus, caution must be exercised in recommending either the pill or an IUD for women at high risk for STDs, ie, those with a variety of sexual partners.

RESURRECTING THE CONDOM

At this point, the reader might be excused for experiencing a sense of futility. Like rising inflation and shortages of energy, the problems outlined earlier seem so immense that nothing short of "restructuring society" (the intellectual equivalent of saying "it ain't no use") would seem to have any effect. A fallacy, though, in considering global problems is to seek all-encompassing solutions. There are no readily available *answers* to the twin problems of pregnancy and STDs in teenagers, but some different *approaches* must be tried. One such that makes immanent sense has been suggested by Felman[11]: promote use of the condom among sexually active teenagers. Can he be serious in recommending resurrection of the old prophylactic that has been the subject of so much locker-room humor through the years? He is indeed! Felman, who is with the Bureau of Venereal Disease Control of the New York City Health Department points out, with impeccable logic:

> The condom is the only device widely

available today that simultaneously provides both effective contraception and protection against STDs. In addition, it can be purchased over the counter at any pharmacy without a prescription. Condoms also completely eliminate major disadvantages of the IUD and the pill—their unwanted and sometimes dangerous adverse effects, the entire burden of which is borne by women.

Some further advantages:

(1) It can be conveniently kept in a pocket or purse for quick use when needed. (2) It is inexpensive, easily within the limits of most teens' financial capabilities. (3) It provides confidence and security to teenagers insecure about possible unwanted results of coitus because it is both a contraceptive and prophylactic. This is most important to teenagers, who often have many different sex partners. (4) The condom places the responsibility for both contracepti[on] and prophylactics on the initiator, generally, of sexual activity, the male. (5) The sexually active woman can carry condoms in her purse to protect herself in a doubtful situation against STDs even if she is already using the IUD or an oral contraceptive.

Felman rightly says: "A major effort by public health authorities and leading physicians to make the advantages of the condom as widely known as its few disadvantages would reap great dividends for STD control as well as reduce the incidence of teenage pregnancies." How can this be accomplished? By education and advertising. The allegation that teenagers will never use condoms can be countered by citing the study of Arnold and Cogswell.[12] They showed that when free condoms were made available to 3,000 teenagers through commercial outlets, usage increased from 20% to 91%.

The prevalent myth about the ineffectiveness of condoms, stemming from faulty products prior to World War II should be countered with data showing that, when properly and consistently used, condoms are now at least 97% effective in preventing pregnancy.[13] As mentioned previously, the story of STDs and the fact that not all of them can be cured (eg, herpes) along with their long-term effects on fertility and perinatal mortality and morbidity must be widely broadcast.

A QUANTUM LEAP

If physicians promoted condom usage in the course of their professional activities (ie, in medical offices, clinics, public health departments, etc) it would constitute a *step* forward in reducing pregnancies and STDs. A quantum *leap* in the campaign, however, would occur if physicians used their influence to encourage mass advertising of condoms. Think of it: no grants, no federal "initiatives," just allow the master of motivation, the American advertising industry, to display its talents.

Felman[11] says:

> The key to the success of such an effort is in persuading the National Association of Broadcasters to allow condom advertising on radio and television and in convincing the copy-review board of newspapers and magazines in general circulation to do the same. The paradox of health values in America today is clearly illustrated by the fact that cigarettes, which are known to cause disease, are prominently advertised in the press, while condoms, which prevent disease, are not considered suitable for advertisements. This practice is responsible for the general public's, especially the teenager public's, continued ignorance concerning the many advantages of the condom.
>
> Organized medicine and public health can take the lead here in changing this by bringing their collective weight to bear on the media to reverse this policy.

It is possible that the appearance of one or two condom advertisements on Monday night football programs would do more to lower teenage pregnancy rates than five years' worth of federally funded adolescent health programs.

Naturally, there will be opposition both from those who believe that contraception is immoral and from those who would like to believe that no sexual activity takes place outside marriage. By advocating condom usage to those who are already sexually active, the physician does not condone promiscuity. Responsible social behavior should be a component of all health education. Those who crusade against all abortions should be challenged to make what, for them, is admittedly a hard choice. Is not prevention of pregnancy preferable to abortion?

Physicians who bear witness to the consequences of unwanted pregnancies and herpes encephalitis must apply the moral yardstick. In this case, inaction amounts to acquiescence. We cannot solve the whole problem, but we have to take some tangible steps in the right direction. In an address to the French bishops, Albert Camus[14] said, "You dream of a world in which no children starve; I dream of a world in which fewer children starve."

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References

1. Dryfoos JG: The incidence and outcome of adolescent pregnancy in the United States. *J Biosoc Sci*, suppl 5, 1978, pp 85-99.
2. Kantner JF, Zelnik M: Contraception and pregnancy: Experience of young unmarried women in the United States. *Fam Plann Perspect* 5:21-35, 1973.
3. Ryde-Bloomquist E: Contraception in adolescence: A review. *J Biosoc Sci* suppl 5, 1978, pp 132-157.
4. Gabrielson MO, Goldsmith S, Stangeland S: Dalkon shield and the young nulliparous patient: Eighteen monthly experience. *Adv Planned Parenthood* 8:138-143, 1973.
5. *STD Fact Sheet, 1978*, ed 34, publication CDC 79-8195. US Dept of Health, Education, and Welfare, 1978, p 22.
6. Non-reported sexually transmitted diseases: United States. *Morbidity Mortality Weekly Rep* 28:61-63, 1979.
7. Corey L: Clinical course and epidemiology of genital herpes, in Holmes KK, Wiesner P (eds): *Non-gonococcal Urethritis and Other Selected Sexually Transmitted Diseases of Public Health Importance. Bull WHO*, to be published.
8. Nahmias AJ, Visintine AM: Herpes simplex, in Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, WB Saunders Co, 1976.
9. Johnson JWC: Gonorrhea in the female, in Rovinsky JJ (ed): *Davis Gynecology and Obstetrics*. New York, Harper & Row Publishers Inc, 1974, vol 2, chap 59.
10. Eshenbach DA, Holmes KK: Acute pelvic inflammatory disease: Current concepts of pathogenesis, etiology, and management. *Clin Obstet Gynecol* 18:35-56, 1975.
11. Felman YA: A plea for the condom, especially for teenagers. *JAMA* 241:2517-2518, 1979.
12. Arnold CB, Cogswell BE: A condom distribution program for adolescents: The findings of a feasibility study. *Am J Public Health* 61:739-750, 1971.
13. Hatcher RA, Stewart GK, Stewart F, et al: *The Condom: Contraceptive Technology 1978-1979*. New York, Irvington, 1978, pp 85-88.
14. Camus A: The unbeliever and Christians: Fragments of a statement made at the Dominican Monastery of Latour-Maubourg in 1948, in *Resistance, Rebellion, and Death*. New York, Modern Library, 1960.

Use of Side-Hole Endotracheal Tube Adapter for Tracheal Aspiration

A Controlled Study

Ehud Zmora, MD, T. Allen Merritt, MD

• **An alternate tracheal aspiration procedure using a side-hole endotracheal adapter was used in conjunction with transcutaneous oxygen (T_cPO_2) monitoring in 13 mechanically ventilated newborn infants. Decline in T_cPO_2 during suctioning and drop in neonatal heart rate were both substantially reduced using a procedure designed to preserve mean airway pressure. When compared with the routine procedure of disconnecting the endotracheal tube from the ventilator and suctioning via an end-hold adapter, this approach prevented precipitous and dangerous hypoxemia.**

(*Am J Dis Child* 134:250-254, 1980)

Endotracheal tube suctioning is an obligatory procedure in patients requiring prolonged mechanical ventilation. This therapeutic procedure is often associated with adverse physiological reactions, including hypoxia,[1,2] apnea, and bradycardia.[3] To our knowledge, no clearly preferential technique has emerged to prevent or ameliorate such adverse reactions.[4] New monitoring techniques, especially transcutaneous oxygen (T_cPo_2) monitoring, are available for more accurate evaluation of different techniques and devices used for endotracheal suctioning.

We report the experience of the infant Intensive Care Nursery at the University of Rochester, NY, using the endotracheal tube adapter with side holes compared with the standard end-hole adapter for endotracheal suctioning in infants requiring endotracheal intubation for mechanical ventilation as assessed by continuous T_cPo_2, neonatal heart rate, and airway pressure monitoring.

MATERIALS AND METHODS

Infants requiring mechanical ventilation (positive peak inspiratory pressure and positive end expiratory pressure [PEEP]) for respiratory distress syndrome, pneumonia, perinatal asphyxia, and gastrointestinal surgery were studied. The infants were intubated with endotracheal tubes with internal diameters of 3.0 and 3.5 mm and they were ventilated using a Baby Bird ventilator. The vacuum source was routine apparatus-Suction Regu-Gage set to generate negative pressure of 40 to 50 mm Hg. Suction catheters, No. 6F and 8F, were used. The suction procedures were performed by the nursing staff as follows: disconnect from ventilator, instillation of

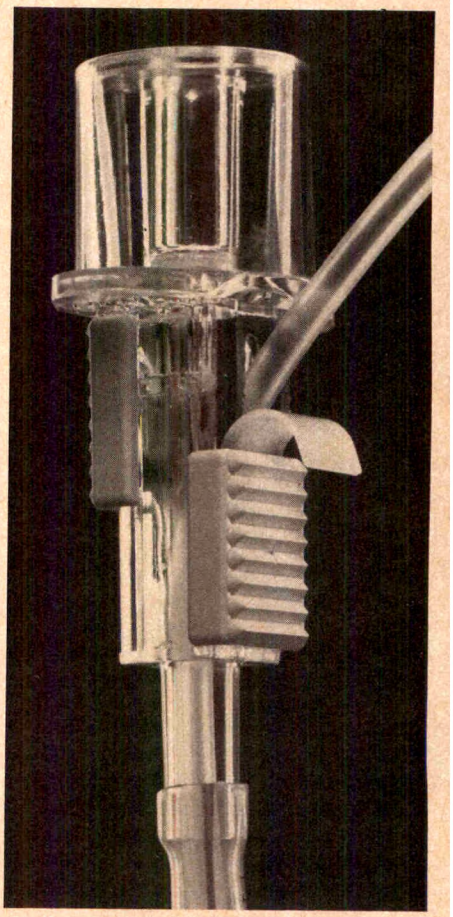

Fig 1.—Side-hole adapter with No. 8F catheter inserted into side-hole for endotracheal tube suctioning.

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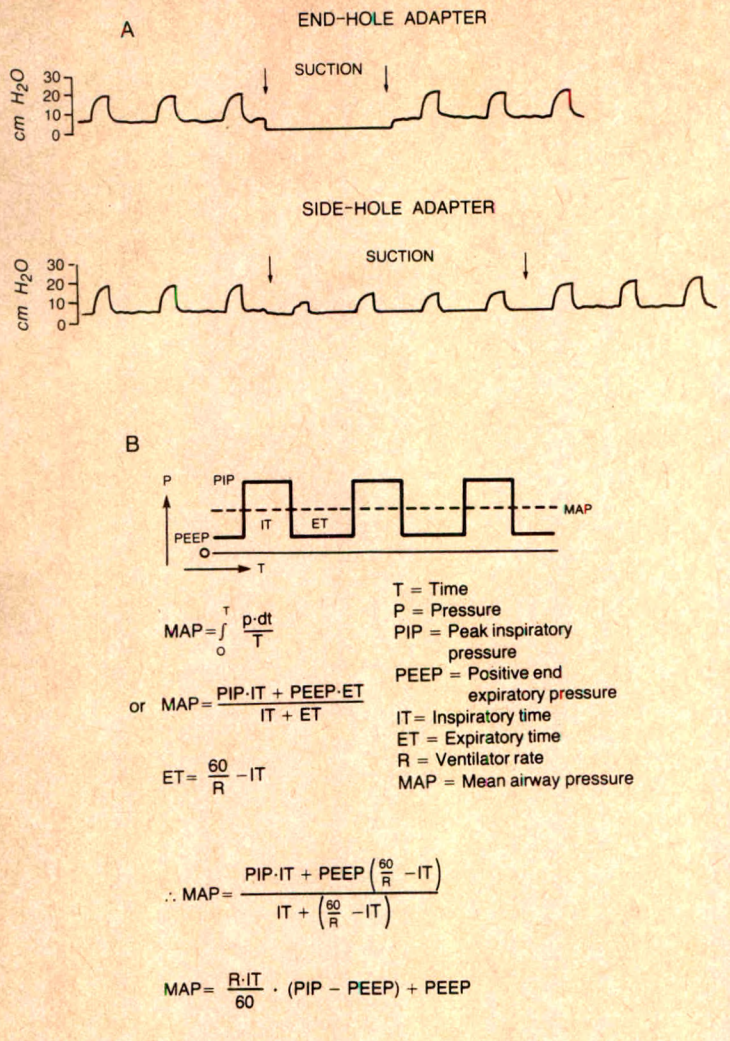

Fig 2.—A, Intermittent mandatory ventilation wave forms with endotracheal tube suctioning. End-hole adapter suctioning reduces pressure to 0 cm H_2O during suctioning procedure while fraction of mean airway pressure remains during side-hole aspiration. B, Mean airway pressure equation.

Table 1.—Transcutaneous Oxygen (T_cPo_2) Alterations Related to Methods of Suctioning

	No. of Procedures in Study		Mean Drop T_cPo_2/ Mean Initial T_cPo_2, mm Hg		Mean % Drop in T_cPo_2		
Patient	End Hole	Side Hole	End Hole	Side Hole	End Hole	Side Hole	P
1	8	8	3/59	1/46	5.9	2.3	NS
	5	5	8/56	5/58	13.9	7.0	NS
2	5	4	6/62	6/66	10.2	9.1	NS
	3	5	9/62	4/67	14.1	5.6	<.01
3	9	5	18/47	6/39	24.9	16.2	<.05
	5	5	11/59	8/67	19.3	12.6	<.01
	5	5	7/50	1/57	13.1	1.4	<.01
4	5	5	3/75	2/75	3.6	2.6	NS
5	5	5	20/70	6/55	28.6	10.9	<.01
6	5	6	11/56	4/76	20.1	5.0	<.01
	5	5	11/59	11/69	18.8	15.6	NS
7	5	5	8/64	6/74	12.8	7.6	<.01
8	5	5	8/52	6/54	16.1	10.7	<.05
9	5	5	4/51	4/48	7.5	7.4	NS
10	5	5	17/109	4/81	15.9	5.4	<.01
11	3	3	11/57	2/71	19.9	3.2	<.01
12	5	5	11/45	5/46	24.2	10.8	<.01
	5	5	8/58	3/61	13.5	4.9	<.01
13	5	5	2/60	3/62	2.3	4.2	NS

0.2 to 0.5 mL (0.9%) saline down the endotracheal tube, 5 s; bagging, 20 s; suction-head turn to the right, ≤ ten s; bagging, 20 s; suction-head turn to the right, ≤ ten s; bagging, 20 s; suction-head turn to the left, ≤ ten s; bagging, 20 s; suction-head turn to the left, ≤ ten s; bagging, 20 s; and reconnection to ventilator and oropharyngeal suction, ten s.

An identical suction procedure at the next scheduled pulmonary toilet, usually one to two hours later, was performed after replacing the endotracheal tube adapter with an endotracheal tube adapter with side holes (Fig 1). Instillation of saline and suctioning were done through the right or left side holes of the adapter, without disconnecting the endotracheal tube from the respirator. Pulmonary inflation during tracheal suctioning using the side-hole adapter was maintained by the Baby Bird ventilator at the same peak inspiratory pressure rate, PEEP, and fraction of inspired oxygen (FIO_2) pressure as preceding the procedure. Infants undergoing tracheal toilet using the end-hole adapter were disconnected from the ventilator during the suctioning procedure and manual inflation of the ventilator bag was performed after reconnecting the infant to the ventilator when presuctioning ventilatory rates were less than 30 breaths/min. When presuctioning ventilation rates were greater than 30 breaths/min, mechanical ventilation was reinstituted at the same rate on reattachment to the ventilator after suctioning. Continuous T_cPo_2 monitoring during all suctioning procedures was done with the Oxymonitor SM 361.

Proximal airway pressures at the level of the endotracheal tube adapter (proximal airway pressure) were measured continuously from a side port T-shaped connecter adapted to the endotracheal tube with a physiological pressure transducer and displayed on a strip chart recorder.

Assuming that the ventilation waveform approximates a square wave configuration (Fig 2, A), mean airway pressure (MAP) was calculated prior to and during the suctioning procedure according to the equation in Fig 2, B.

For every paired study on each baby, tracheal aspirations were performed by the same nurse who alternately used the regular end-hole adapter and the side-hole

adapter. The same monitor was used for determining neonatal heart rate and recording this simultaneously with the airway pressure wave forms. This study was reviewed and approved by the Committee for the Protection of Human Subjects at the University of Rochester.

RESULTS

Thirteen babies with gestational ages from 27 to 40 weeks and birthweights ranging from 900 to 4,400 g who required tracheal aspiration as a part of routine clinical care were included in 19 paired studies. Table 1 lists the number of procedures and the decrease in T_cPo_2 during suctioning using both the end-hold and side-hole adapter. Percent decline in T_cPo_2 during each procedure was calculated and the mean of all procedures was tabulated in Fig 3. In all but two studies, percent decrease in T_cPo_2 was less using the side-hole adapter. The magnitude of these differences was significantly less ($P < .01$) in 12 of 19 studies on all occasions. In an attempt to explain these differences, MAPs resulting from the suctioning procedures were calculated. Mean airway pressures remained higher when using the side-hole vs the end-hole endotracheal tube adapter. As given in Table 1, proximal airway pressures dropped to 0 cm H_2O using the end-hold adapter during suctioning when the tube was disconnected from the ventilator. When using the side-hole adapter, a fraction of the MAP was maintained. A comparison between the percent decrease in T_cPo_2 and the decline in MAP for both suctioning routes is given in Table 3. These data clearly indicate that in 17 or 18 paired studies, the greater the decrease in MAP, the more severe was the decline in T_cPo_2.

The importance of these findings as seen in Fig 4 indicates that in our 18 infants the percent decrease in T_cPo_2 as related to the simultaneous drop in MAP was substantially greater in infants in whom end-hole endotracheal tube suctioning was used. Occurrence of bradycardia was significantly less ($P < .01$) in six infants, not different in 11, and considerably worse in one infant when the side-hole adapter was compared with the end-hole suctioning (Fig 5).

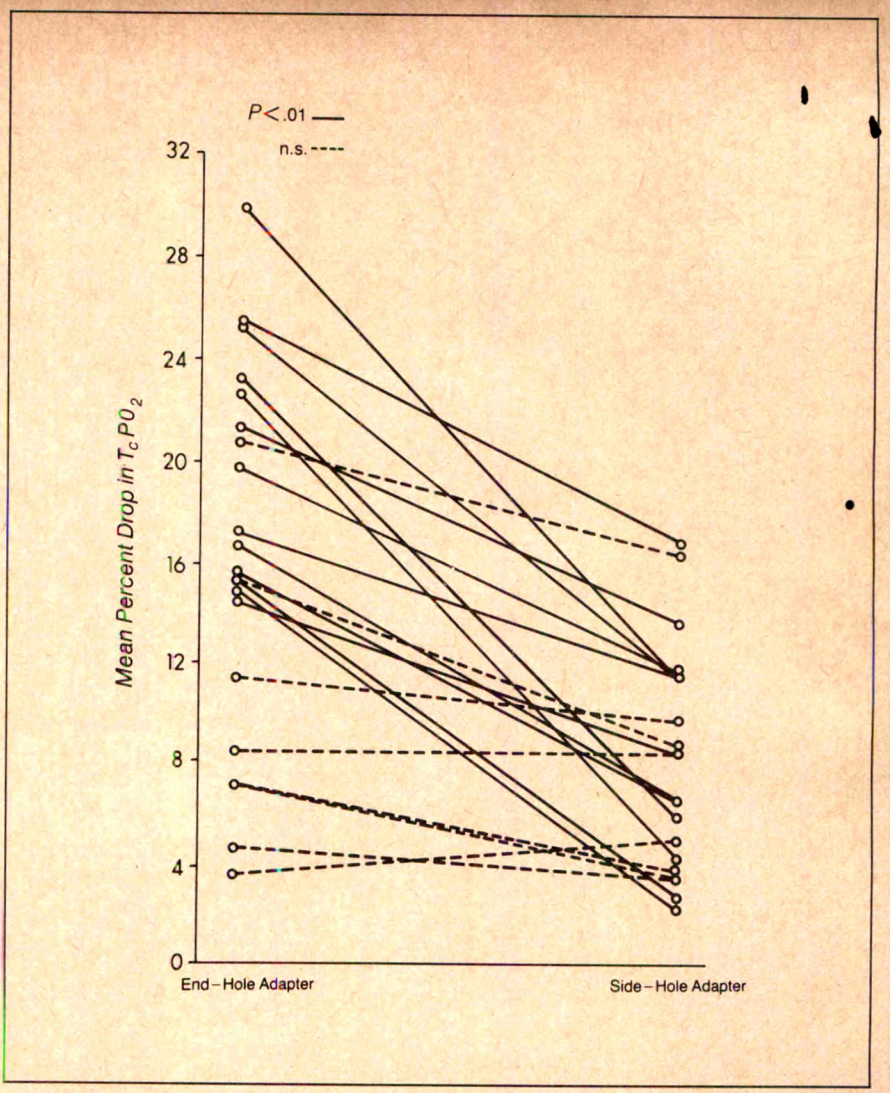

Fig 3.—Comparison of percent drop in transcutaneous oxygen (T_cPo_2) in 19 paired tracheal aspiration studies (194 procedures). Solid lines indicate substantial reduction in percent decrease of T_cPo_2 using side-hole adapter. Broken lines indicate decrease that was not statistically significant.

Table 2.—Mean Airway Pressure (cm H_2O) in Endotracheal Tube Adapter (Proximal Airway Pressure)

	End-Hole Adapter		Side-Hole Adapter	
Patient	Before Suction Procedures	During Suction Procedures	Before Suction Procedures	During Suction Procedures
1	20.8	0	20.8	9.2
2	3.6	0	3.6	2.7
	3.0	0	3.0	2.2
3	13.9	0	11.5	7.7
	8.3	0	8.3	5.7
	7.2	0	7.2	5.2
4	6.8	0	6.8	3.8
5	9.9	0	9.9	7.6
6	8.2	0	8.2	5.8
	5.2	0	5.2	2.9
7	6.0	0	6.0	2.9
8	8.0	0	8.0	4.1
9	6.7	0	6.7	2.7
10	16.8	0	17.2	8.0
11	8.7	0	8.7	5.5
12	11.7	0	11.7	7.6
	12.0	0	11.0	8.7
13	3.9	0	3.9	1.9

Table 3.—Relationship Between T_cPo_2 and Decrease in MAP*

Patient	End-Hole Adapter: Drop in MAP, cm H_2O	End-Hole Adapter: % Drop in T_cPo_2	Side-Hole Adapter: Drop in MAP, cm H_2O	Side-Hole Adapter: % Drop in T_cPo_2
1	20.8	13.9	11.6	7.9
2	3.6	10.2	0.9	9.1
	3.0	14.1	0.8	5.6
3	13.9	24.9	3.8	16.2
	8.3	19.3	2.6	12.6
	7.2	13.1	2.0	1.4
4	6.8	3.6	3.0	2.6
5	9.9	28.6	2.3	10.9
6	8.2	20.1	2.4	5.0
	5.2	18.8	2.3	15.6
7	6.0	12.8	3.1	7.6
8	8.0	16.1	3.9	10.7
9	6.7	7.5	4.0	7.4
10	16.8	15.9	9.2	5.4
11	8.7	19.9	3.2	3.2
12	11.7	24.2	4.1	10.8
	12.0	13.5	2.3	4.9
13	3.9	2.3	2.0	4.2

*T_cPo_2 indicates transcutaneous oxygen; MAP, mean airway pressure.

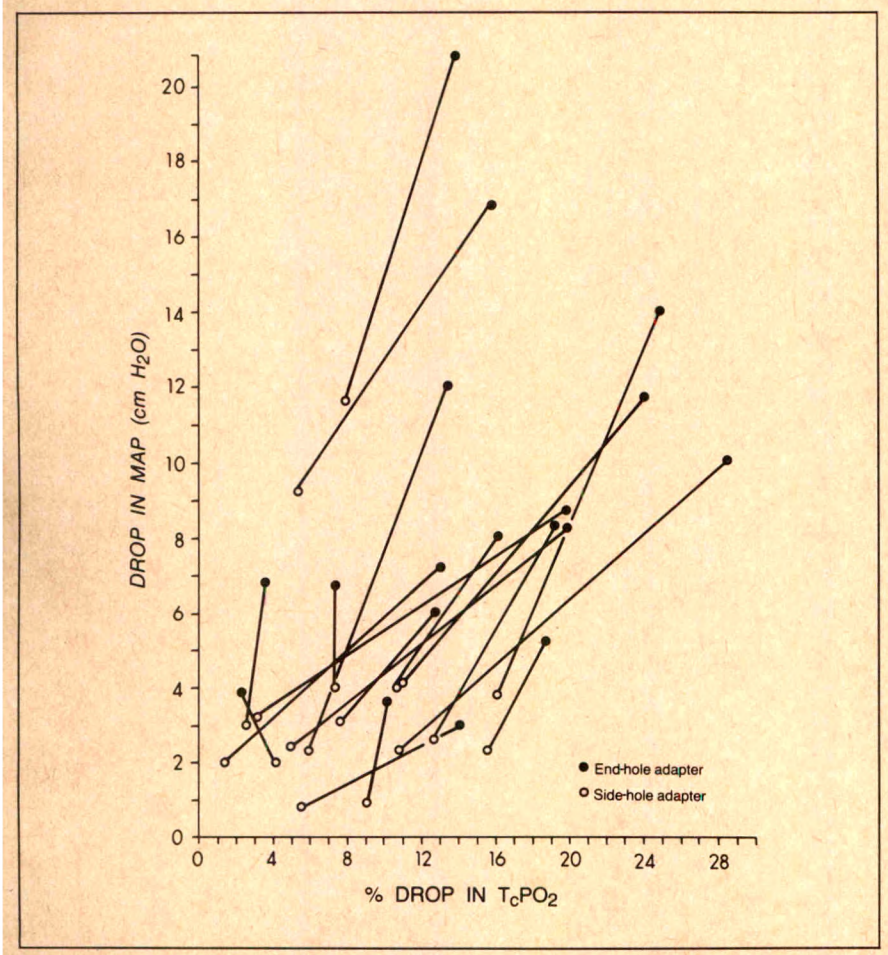

Fig 4.—Decline in transcutaneous oxygen (T_cPo_2) associated with endotracheal tube aspiration compared to decrease in mean airway pressure in 18 paired studies (178 procedures). Greater decrease in mean airway pressure, more pronounced decline in T_cPo_2.

COMMENT

A host of disturbing complications has been reported in association with neonatal endotracheal tube suctioning. Pneumothorax,[5] bronchial perforation,[6] atelectasis,[7] apnea,[8] hypoxemia,[2] and bradycardia[3] have been reported in preterm and term infants undergoing endotracheal tube aspiration.

Fox et al[9] documented substantial decreases in Pao_2 after suctioning accompanied by diminished inspiratory and expiratory resistance that only returned to normal after a period of hyperventilation. The same authors found reduced lung volume suggestive of atelectasis that may prolong the period of recovery from tracheal airway aspiration. Chest percussion and postural drainage have been reported to elevate Pao_2[10] in infants after suctioning, yet the amount of secretions removed by physiotherapy or tracheal aspiration has not been correlated to improvements in T_cPo_2 or promptness in resolution of pulmonary disease.[11] Recently, the benefits of frequent airway suctioning have been questioned, and current nursery techniques may require modification.

Long et al[12] demonstrated substantial drops in T_cPo_2 levels in preterm and term infants undergoing pulmonary toilet. Using a side-hole endotracheal tube adapter, Cabal and associates[13] found a smaller drop in oxygen saturation and less bradycardia. Stimulation of pulmonary irritant reflexes by the suction catheter may account for apnea[11] and frequently is associated with bradycardia. Anticipation of hypoxemia often encourages the use of either preoxygenation or hyperventilation, yet the advantages of the latter approach have not been thoroughly studied.

Our findings of diminished decrease in T_cPo_2 in the controlled use of side-hole endotracheal tube aspiration as compared with ventilator disconnection and end-hole aspiration result from maintenance of MAP throughout the procedure. Mean airway pressure has been shown to inversely correlate to the magnitude of the alveolar-arterial oxygen gradient[14] and to a useful clinical measure of pressures transmitted to the airway.[15] By

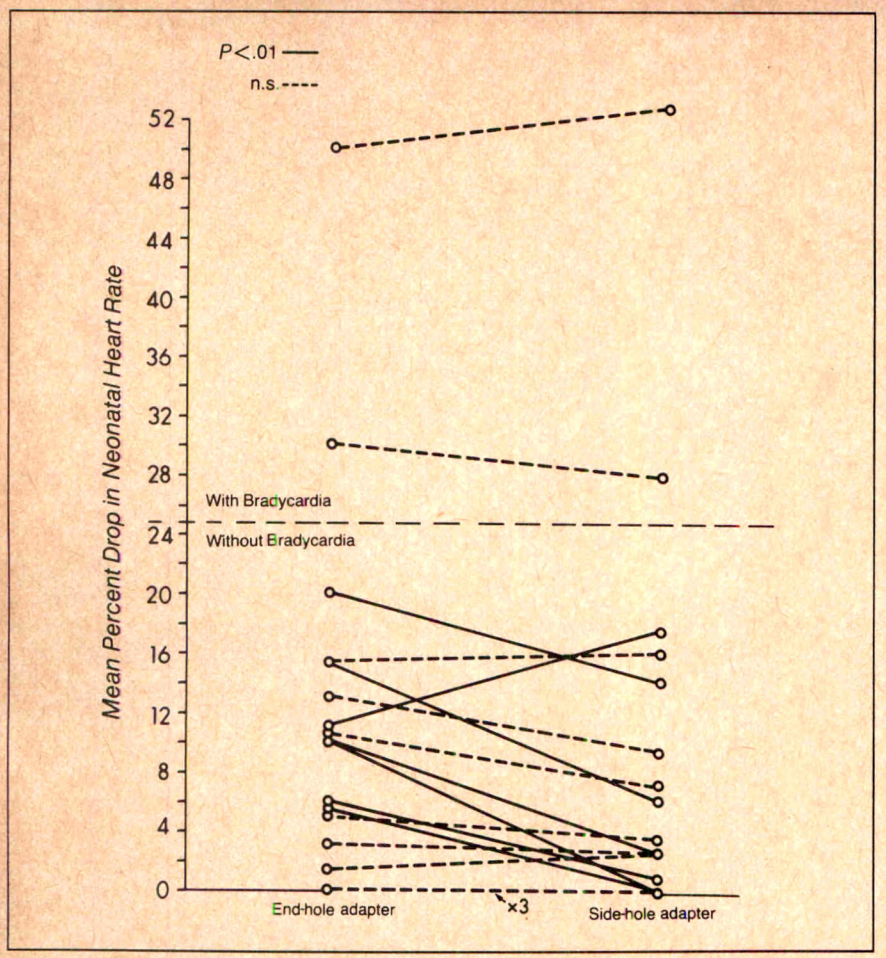

Fig 5.—Comparison of decrease in neonatal heart rate using both suctioning techniques in 18 paired tracheal aspiration studies (178 procedures). Less drop in neonatal heart rate was observed when side-hole adapter was used for suctioning.

retaining a portion of presuctioning airway pressure during tracheal aspiration using our technique, T_cPo_2 remained within acceptable ranges making preoxygenation unnecessary.

Although the drop in neonatal heart rate was diminished in some infants undergoing tracheal aspiration using the side-hole technique, no improvement in the heart rate was observed in most infants. This may suggest that pulmonary irritant receptors, rather than hypoxemia, play a major role in heart rate decrement during suctioning.[16]

The side-hole endotracheal tube adapter is not without disadvantages. The time required for introducing the suction catheter into the endotracheal tube is slightly longer. Furthermore, the need to turn the infant's head from side to side requires the service of two persons to maintain a stable airway-ventilator hose combination. In spite of these disadvantages, our experience suggests that hypoxemia can be minimized by our technique. There is a need to compare proximal and distal airway pressures using this technique to determine whether change in T_cPo_2 reflect alterations of pressures within the lung. Furthermore, continued studies are warranted during the acute and convalescent stages of a variety of pulmonary diseases in infants and children.

Assistance was provided by the nursing staff of the Intensive Care Nursery and by Larry Ten Eyke AART, of the Respiratory Therapy Department, University of Rochester, Rochester, NY. Corometrics 512 Neonatal Monitors were provided by Craig Castle. The endotracheal tube adapter with side holes (Neonatal C/D Adapters) was provided by Novametrix, Medical Systems Inc, Wallingford, Conn.

References

1. Huch R, Lucey JF, Huch A: Oxygen: Noninvasive monitoring. *Perinatal Care* 2:18-25, 1978.
2. Mackenzie CF, Shin B, McAslan TC: Chest physiotherapy: The effect on arterial oxygenation. *Anesth Analg* 57:28-30, 1978.
3. Cordero L Jr, Hon EH: Neonatal bradycardia following nasopharyngela stimulation. *J Pediatr* 78:441-447, 1971.
4. Mellins RB: Pulmonary physiotherapy in the pediatric age group. Proceedings of the Conference on the Scientific Basis of Respiratory Therapy. *Am Rev Resp Dis* 110(suppl):137-142, 1974.
5. Vaughau RS, Menke JA, Gracora GP: Pneumothorax: A complication of endotracheal tube suctioning. *J Pediatr* 92:633-634, 1978.
6. Anderson KD, Chandra R: Pneumothorax secondary to perforation of sequential bronchi by suction catheters. *J Pediatr Surg* 11:687-693, 1976.
7. Brandstater B, Muallem M: Atelectasis following tracheal suction in infants. *Anesthesiology* 31:468-473, 1969.
8. Downes JJ, Wilson JF, Goodson D: Apnea, suction, and hyperventilation: Effect on arterial oxygen saturation. *Anesthesiology* 22:29-33, 1961.
9. Fox WW, Schwartz JG, Shaffer TH: Pulmonary physiotherapy in neonates: Physiologic changes and respiratory management. *J Pediatr* 92:977-981, 1978.
10. Finer NN, Boyd DPT: Chest physiotherapy in the neonate: A controlled study. *Pediatrics* 61:282-285, 1978.
11. Etches PC, Scott B: Chest physiotherapy in the newborn: Effect on secretions removed. *Pediatrics* 62:713-715, 1978.
12. Long JG, Philip AGS, Lucey JF: Use of continuous T_cO_2 monitoring to avoid handling and pain as causes of hypoxemia. *Pediatr Res* 13:499, 1979.
13. Cabal LA, Devaskar SU, Plajestek C, et al: An improved technique for airway suctioning. *Pediatr Res* 13:532, 1979.
14. Herman S, Reynolds EOR: Methods for improving oxygenation in infants mechnically ventilated for severe hyaline membrane disease. *Arch Dis Child* 48:612-617, 1973.
15. Boros SJ: Variations in inspiratory: expiratory ration and airway pressure wave form during mechanical ventilation: The significance of mean airway pressure. *J Pediatr* 94:114-117, 1979.
16. Fleming PJ, Bryan AC, Bryan MH: Functional immaturity of pulmonary irritant receptors and apnea in newborn preterm infants. *Pediatrics* 61:515-518, 1978.

Sexual Abuse of Boys

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• **In a retrospective review of 145 sexually abused children, 11% were male. The boys were more likely to be assaulted in a public place than were girls, and boys were more prone to physical injury. The relationship of the perpetrator to the child was similar for boys and girls as was the age of the children. This study emphasizes the existence of boys as victims of sexual abuse.**

(*Am J Dis Child* 134:255-257, 1980)

Recognition of physical abuse of children has dramatically improved since its description in the medical literature in the early 1960s.[1] However, recognition and treatment of sexually abused children has been less aggressive.[2] In the literature, the media, and the clinical setting, sexual abuse is usually stereotyped as a male perpetrator and a female victim. This study seeks to assess the importance of male children as victims of sexual abuse and to determine whether or not they pose problems different from those of girls as victims.

METHODS

A chart review was conducted for each patient coming to the Children's Hospital of Buffalo emergency room in the period from Jan 1, 1976, to Dec 31, 1978, with a chief complaint related to sexual abuse. The population served by the emergency room is preponderantly urban. The patient histories, physical examination, and specimen collection for laboratory procedures were performed by resident physicians in obstetrics and gynecology for the female patients and by pediatric residents for the male patients. Each was carried out according to a protocol, with special forms for recording the history, the results of the physical examination, the documentation of evidence collection, the methods of treatment, and the results of follow-up.

The review addressed the following aspects: the age and sex of the patient, the relationship of the patient to the alleged perpetrator, the location at start of the episode, physical findings suggesting injury of a sexual nature, physical findings suggesting injury of a nonsexual nature, and laboratory findings including presence and location of spermatozoa as well as results of tests on serologic and culture specimens taken. Male and female patients were compared with respect to the victim's age, relationship of the perpetrator and the victim, and the presence of positive physical findings or laboratory results. For this review, sexual abuse is defined as "the exposure of a child to sexual stimulation inappropriate for the child's age, level of psychosocial development, and role in the family."[3]

RESULTS

One hundred seventy patients younger than 21 years old presented as victims of sexual abuse. There were 154 female patients (91%) and 16 male patients (9%). There were 50 cases in 1976 (8% boys), 52 cases in 1977 (6% boys), and 68 cases in 1978 (13% boys). Of the 170 patients in the study, 145 gave histories consistent with the chief complaint. Of the other 25 cases, all of whom were girls, eight were situations of adolescent sexual activity by mutual consent, but arousing parental concern. The other 17 cases had insufficient data or did not meet the criteria to be considered a case of sexual abuse. All 16 boys' histories were consistent with the definition of sexual abuse used in this study. Therefore, of the 145 patients with histories of sexual abuse, 16 (11%) were male and 129 (89%) were female.

Male patients ranged from 3.3 to 16.4 years of age, with a mean age of 9.7 years. Female patients ranged in age from 0.3 to 20.2 years of age, with a mean age of 10.2 years. The relationships between the patients and the perpetrators are presented in Table 1. All the perpetrators were male for both male and female patients.

Table 2 describes the male patients. Of the 16 male patients, 14 had adequate information to determine where the incident began. Five cases (36%) occurred at home, and nine (64%) began in a public place (eg, street or park). Of the 129 female patients' records, 120 were adequate to indicate where the incident began. Of these, 44 cases (36.6%) occurred at home, 38 (31.6%) began in other familiar places (eg, the home of a friend or relative) and 38 (31.6%) began in a place of public access.

Eight of the 16 boys (50%) had positive findings on physical examination. Seven boys had evidence of anal

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or perianal trauma. Patient number 5 had evidence of recent abrasions, but not in the genital or anal area. Two of the seven boys with anal trauma also demonstrated multiple ecchymoses on other parts of their bodies. Only one boy had spermatozoa present in the rectum; there was no semen recovered from the oral cavity of any of the boys. None of the boys had cultures positive for gonorrhea or a positive VDRL when seen at follow-up. Forty-seven of the girls (36%) had positive findings on physical or laboratory examination. Fourteen of these girls demonstrated injuries only in nongenital areas.

COMMENT

Historically, widely varying cultural attitudes have determined concepts of sexual abuse. In Western society, there is currently some professional consensus regarding the term. The definition applied in this study for review of cases[3] is not unlike that of Kempe[2]: "the involvement of dependent, developmentally immature children and adolescents in sexual activities that they do not fully comprehend, to which they are unable to give informed consent, or that violate the social taboos of family roles." Within that context, however, available studies give little attention to the male child as an entity distinct from girls who are victims of sexual abuse.[4-7] By emphasizing diagnosis and management of cases of female patients with no mention of male patients beyond their incidence, the victim of sexual abuse is implicitly stereotyped as female while the assailant is portrayed as male.

Table 1.—Relationships of Perpetrators to Victims

Perpetrators	No. (%) Boys (n = 16)	No. (%) Girls (n = 129)
Stranger	9 (56)	57 (44)
Family member	2 (13)	32 (25)
Babysitter	1 (6)	8 (6)
Others known to patient	4 (25)	32 (25)

The current study is biased by the fact that patient selection was based on initial complaint and not final diagnosis. As such, only children with overt complaints of sexual maltreatment were able to be identified. This procedure may have selected a patient population with a higher frequency of positive findings. Children who come to medical attention because of vaginal or urethral discharge, abdominal pain, or behavioral symptoms and who are subsequently found to have been sexually abused are an important group, but they could not be identified in this study. Because obstetric-gynecology residents examined the female patients and pediatric residents examined the male patients, artificial differences in historical and physical findings between boys and girls may have been created.

In this study, boys accounted for 11% of those children giving a history of sexual abuse. This percentage is similar to that reported by deFrancis[8] in 1969 in which 16% of children appearing as victims of sexual abuse were male. Jaffe et al[4] reviewed sexual offense complaint records of the Minneapolis Police Department for 1970 and found that 12% of the victims younger than 16 years old were male. Copeland et al[9] reported that 14% of the victims in their study were male. In the latter two reports, as in our own, the patients presented explicitly as victims of sexual abuse. The incidence of fortuitously discovered covert victims of sexual abuse is not well known, although it is interesting that a similar percentage in a study of children with gonorrhea were male (15 of 100 children 14 months to 14 years old).[10] Why a higher proportion of sexual abuse victims are not male is not known. Brant and Tisza[3] ask whether there are indeed fewer male victims or if "other factors contribute to males seeking attention less often."

As noted in this study, the sexual abuse itself results in physical trauma

Table 2.—Features of Male Patients

Patient/ Agr, yr	Perpetrator	Site Where Incident Began	Genital Injury	Nongenital Injury
1/6.8	13-year-old male living in victim's home	Home	Perianal abrasions	. . .
2/7.4	Natural father	Home	. . .	. . .
3/3.3	Foster brother	Foster home	. . .	. . .
4/10.5	Male stranger	Street	Anal hematoma	Left parietal ecchymosis
5/9.3	Male stranger	Street	. . .	Bilateral wrist abrasions
6/13.5	Male stranger	Street/car	Perianal abrasion	. . .
7/7.7	Male stranger	Home	Perianal lacerations*	. . .
8/16.4	3 male strangers	Parking lot	Perianal abrasion and ecchymosis	Multiple trunk and extremity ecchymoses
9/10.0	18-year-old male family friend	Home	. . .	. . .
10/9.7	Man known to victim's parents	Uncertain	. . .	. . .
11/13.6	Man known to victim	Street/garage	. . .	. . .
12/5.9	Male stranger	Street	Anal laceration	. . .
13/7.4	16-year-old male babysitter	Uncertain	. . .	. . .
14/8.6	Male stranger	Street	Anal laceration	. . .
15/9.2	Male stranger	Street	. . .	. . .
16/16.3	Male stranger	Park	. . .	. . .

*Motile sperm present in rectum.

of a large percentage of the boys. Others have reported sexual abuse precipitating gonorrhea,[10] herpes genitalis,[11-13] syphilis,[14] group B streptococcal infection, chancroid, lymphogranuloma venereum, lymphogranuloma inguinale, pubic lice, scabies,[15] presence of foreign bodies,[4] the traumatic lesions of coexisting (nongenital) child abuse,[4,16] and death by asphyxiation.[17] Psychoemotional sequellae are less clear-cut. Kempe[2] believed that boys suffer greater psychological trauma than girls. Glueck[18] noted that almost one half of all pedophiliacs experienced sexual abuse as boys. Behavioral changes after recurrent sexual abuse by parents have been reported.[19] Yet others temper their impression of the psychoemotional impact and speak of children in general, saying behavioral changes are variable, complex, multifactorial, often not immediately evident, and still the subject of much study.[20]

There are no differences between boys and girls with respect to the age at which the child comes to the attention of the health professional or with respect to the sex of the perpetrator. Since it was not consistently determined for how long the sexual abuse was allowed to continue before seeking help, it is unknown whether sexual abuse of boys remains covert, and therefore unresolvable, for longer periods than for girls. The current study is consistent with those of deFrancis[8] and Jaffe et al[4] as to the age of the victims.

Seven of the 16 boys (44%) knew their assailant. This is not statistically significantly different from the girls (56%). Most studies agreed that a majority of the patients know their assailants.[8,21,22] Two thirds of the boys' abusive incidents began in a place of public access. Only one third of the girls' incidents began in a public place. That the incident began in a public place did not necessarily mean that the assault was completed there, but this describes the location in which the child was vulnerable. Because of the small size of our male cohort, we are unable to determine if the higher percentage of boys abused in public places is truly characteristic of boys as victims.

Eight of our 16 male patients (50%) demonstrated genital or nongenital injuries. This is a high incidence in comparison with girls or children in general in other studies. In a project reviewing adult women and girls in Washington, DC, by Hayman and Lanza,[23] 7.1% of the children had major injuries (combined genital and nongenital), but the authors did not quantitate or characterize the minor injuries. In Voigt's study,[22] serious injury of girls younger than 15 years old was unusual, occurring in only 0.7%. Injuries to boys are not mentioned.

The high percentage of injuries in our study is mostly contributed by anal or perianal lesions. The anus is the only readily available orifice in the male perineum. It is also of smaller caliber than the mouth or female vagina. Paul[16] described the shearing force required to insert a penis into the previously unviolated anus of a young child as sufficient "to rupture the delicate and poorly supported blood vessels at the anal verge," producing local hematoma and swelling. Depending on the force and repetition applied, tearing of anal structures may occur.

It is important to remember that 50% of the boys and 64% of the girls demonstrated no physical or laboratory evidence of sexual contact. If the physician relies on objective findings to confirm a diagnosis of sexual abuse, the majority of these children might not receive appropriate intervention and treatment.

IMPLICATIONS

This study suggests that boys are more commonly victims of sexual abuse than is generally appreciated. Boys are similar to girls in the type of perpetrator who assaults them and in the age group at which they appear for medical examination. Although they are equally prone to assault in their own homes, boys are more likely to be assaulted in public places and more likely to be physically injured by the incident. Parents, health care providers, and child advocates need to be alerted to the existence of the male child sexual abuse victim so that prevention and timely intervention can be provided. In evaluating traumatic injuries, genital infections, and psychoemotional disorders in boys of any age, the possibility of sexual abuse must be considered.

References

1. Kempe CH, Silverman FN, Steele BF, et al: The battered child. *JAMA* 181:17-24, 1962.
2. Kempe CH: Sexual abuse, another hidden pediatric problem: The 1977 C. Anderson Aldrich Lecture. *Pediatrics* 62:382-389, 1978.
3. Brant RST, Tisza VB: The sexually misused child. *Am J Orthopsychiatry* 47:80-90, 1977.
4. Jaffe AC, Dynneson L, ten Bensel RW: Sexual abuse of children. *Am J Dis Child* 129:689-692, 1975.
5. Rosenfeld AA, Drieger MJ, Nadelson C, et al: The sexual misuse of children: A brief survey. *Psychiatr Opin* 13:6-12, 1976.
6. Schultz LG: The child sex victim: Social, psychological and legal perspectives. *Child Welfare* 52:147-157, 1973.
7. Herjanic B, Wilbois RP: Sexual abuse of children. *JAMA* 239:331-333, 1978.
8. DeFrancis V: *Protecting the Child Victim of Sex Crimes Committed by Adults*. Denver, American Humane Association, 1969.
9. Copeland L, Harrer M, Brody J, et al: *Sexual Abuse of Children*. San Francisco, Queen's Bench Foundation, 1976.
10. Nelson JD, Mohs E, Dajani AS, et al: Gonorrhea in preschool and school-aged children. *JAMA* 236:1359-1364, 1976.
11. Nahmias AJ, Dowdle WR, Naib ZM, et al: Genital infection with *Herpesvirus hominis* types 1 and 2 in children. *Pediatrics* 42:659-666, 1968.
12. Jaffe AC: Sexual abuse and herpetic infections in children. *J Pediatr* 89:338, 1976.
13. Shturman-Ellstein R, Borkowsky W, Fish I, et al: Myelitis associated with genital herpes in a child. *J Pediatr* 88:523, 1976.
14. Ackerman AB, Goldfaden G, Cosmides JC: Acquired syphilis in early childhood. *Arch Dermatol* 106:92-93, 1972.
15. Grossman M, Drutz DJ: Venereal disease in children. *Adv Pediatr* 21:97-137, 1974.
16. Paul CM: The medical examination in sexual offenses against children. *Med Sci Law* 17:251-258, 1977.
17. Sgroi SM: Sexual molestation of children: The last frontier in child abuse. *Child Today*, May-June 1975.
18. Glueck RC: Pedophilia, in Slovenko R (ed): *Sexual Behavior and the Law*. Springfield, Ill, Charles C Thomas Publisher, 1965, pp 539-562.
19. Weeks RB: The sexually exploited child. *South Med J* 69:848-850, 1976.
20. Burgess AW, Groth AN, Holmstrom LL, et al: *Sexual Assault of Children and Adolescents*. Lexington, Mass, Lexington Books, 1978.
21. Swanson DW: Adult sexual abuse of children. *Dis Nerv Sys* 29:678-683, 1968.
22. Voigt J: Sexual offenses in Copenhagen: A medicolegal study. *Forensic Sci* 1:67-76, 1972.
23. Hayman CR, Lanza C: Sexual assault on women and girls. *Am J Obstet Gynecol* 109:480-486, 1971.

Treatment of Bartter's Syndrome With Indomethacin

Eduardo H. Garin, MD; Robert S. Fennell III, MD; Abdollah Iravani, MD; George A. Richard, MD

• Two patients with Bartter's syndrome were treated with indomethacin (2 mg/kg/day). The administration of the drug resulted in weight gain; a decrease in the rate of urinary excretion of sodium and inorganic phosphate suggesting an increase in proximal tubular reabsorption; an increase in serum potassium concentration, with a transient decrease in the rate of urinary potassium excretion in one patient; and a decrease in plasma renin activity and in the rate of urinary aldosterone excretion. Since indomethacin has been shown to inhibit prostaglandin synthetase, these observations support the hypothesis that prostaglandin excess is a basic pathogenic mechanism in Bartter's syndrome.

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Bartter's syndrome is defined as the association of hypokalemia, metabolic alkalosis, hyperaldosteronism, hyperreninemia, normal blood pressure, and hyperplasia of the juxtaglomerular apparatus.[1]

Although the clinical, biochemical, and histologic findings have been well defined, the pathogenesis of the disease has remained obscure. Reversal of the abnormal findings with prostaglandin synthetase inhibitors (indomethacin,[2-6] aspirin,[6,7] ibuprofen,[5,6] naproxen[8]) has suggested a pathogenic role for prostaglandins. We describe two patients with Bartter's syndrome who underwent a clinical trial of indomethacin to test the hypothesis that prostaglandin excess is a basic pathogenic mechanism in these patients.

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SUBJECTS AND METHODS

Two patients who fulfilled the diagnostic criteria for Bartter's syndrome were admitted to the Clinical Research Center, W. Shands Teaching Hospital, Gainesville, Fla.

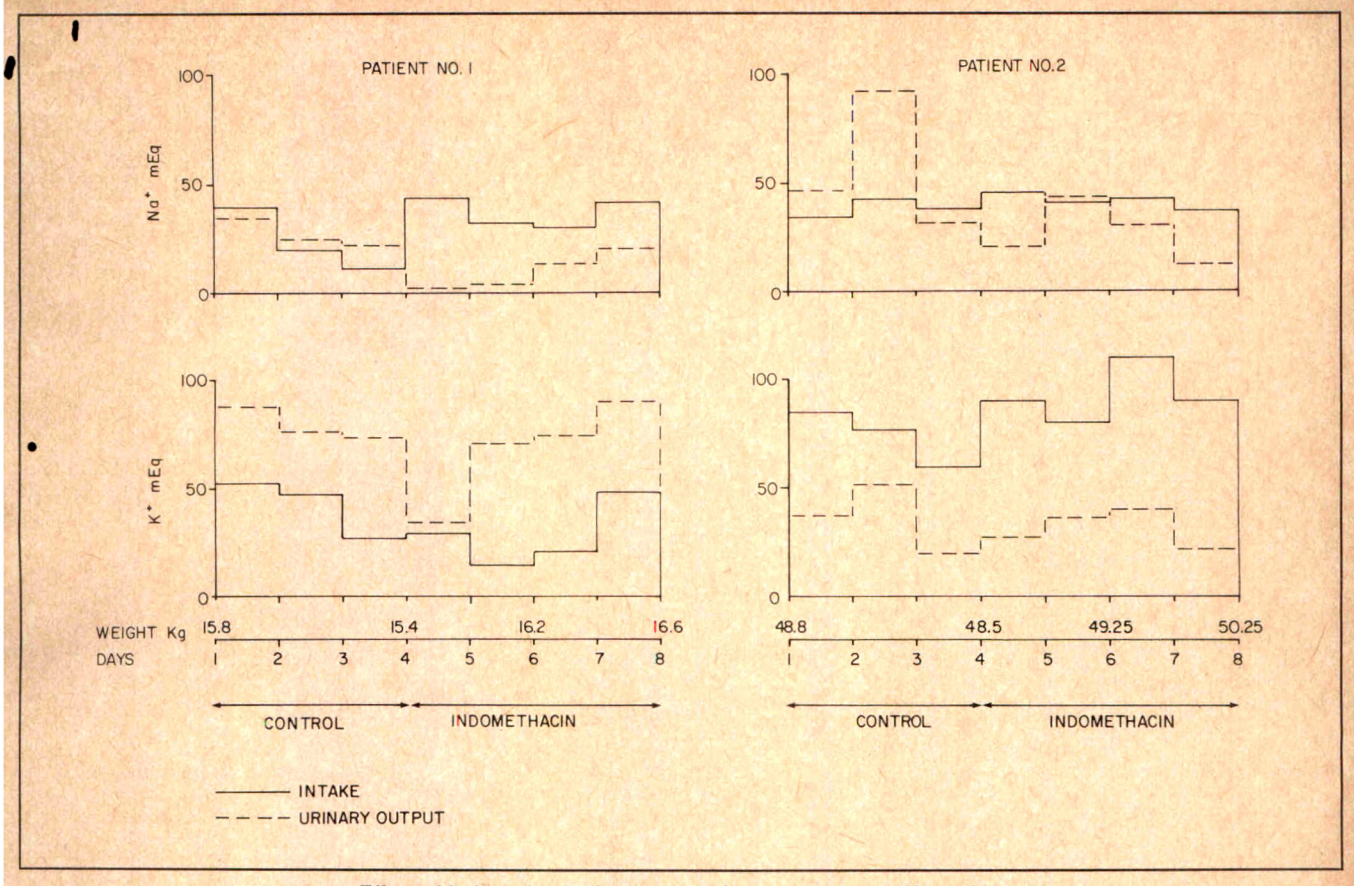
Patient 1 was a 7-year-old girl who was initially hospitalized because of seizures at age 2 weeks. At that time, polydypsia and polyuria were noted. Subsequent follow-up showed poor growth, persistence of the polyuria and polydypsia, constipation, and hypokalemia. For the first 5 years of life, she was treated only with potassium supplements. Because of persistence of symptoms, and a serum potassium level of 2.7 mEq/L, triamterene was given in a dosage of 4 mg/kg/day together with potassium supplements. One month later, because of bone demineralization, calcium supplements and cholecalciferol (vitamin D_3) (5,000 units/day) were started. Despite these efforts, she had rickets, bone pain, and persistent hypokalemia develop. A one-month course of propranolol hydrochloride (2 mg/kg/day) did not affect these clinical and biochemical abnormalities. At age six, she had tetany develop that was controlled with intravenous calcium gluconate infusion; cholecalciferol dosage was increased to 30,000 units a day. The rachitic lesions healed although she continued to have hypokalemia, polyuria, polydypsia and her height and weight remained below the third percentile.

Patient 2 was an 18-year-old man who was recognized to be small for age and to have had polydypsia at age 7 months. Hyposthenuria and hypokalemia were first noted when he was 5 years old, and he was treated with hydrochlorothiazide and potassium supplements. During the subsequent year, there was no improvement in his symptoms; his serum potassium level was 2.1 mEq/L. He was given a low-salt diet and potassium supplements. Three years later, because of persistent hypokalemia, triamterene (100 mg twice daily) and potassium salts were given with inconsistent results. His serum potassium level varied during the succeeding years from 3.1 to 3.8 mEq/L, and there was no improvement in his growth rate and polyuria. Nephrocalcinosis was noted at age 14 years. At age 17 years, he had a growth spurt associated with sexual maturation, which brought him up to the fifth percentile in height.

Informed consent was obtained prior to the study. All medications except potassium supplements were discontinued for one week prior to admission. Patients were offered a diet calculated to supply 50 mEq of sodium daily. Potassium in the food amounted to 32 mEq/day for patient 1 and 40 mEq/day for patient 2. The food was weighed, and data in the US Department of Agriculture's *Handbook No. 8* were used to calculate sodium and potassium.[9] Fluids were given ad libitum and caloric intake was held constant. Amounts of potassium supplements were recorded daily.

During a three-day control period and during a subsequent four-day period of indomethacin therapy, 24-hour urine collections were obtained. Indomethacin was administered in a dosage of 2 mg/kg/day given in three divided doses with meals.

Serum samples were obtained with the patients fasting and in the supine position on days 1, 4, and 6 and at the completion of the study on day 8. Serum and urine samples were analyzed for sodium, potassium, inorganic phosphate, calcium, and creatinine with an automated system of chemical analysis. Blood was obtained on days 1 and 8 for plasma renin and parathyroid hormone (PTH) tests, which were determined by radioimmunoassay. Venous blood pH and plasma base excess were determined on days 4 and 8. Urine collected on days 1 and 7 was analyzed for aldosterone. Fractional excretions (F_Es) of sodium, potassium, calcium, and inorganic phosphate were determined on days 1, 4, 6, and 8. Fractional excretion represents the fraction of a filtered solute that is excreted, and it is thus inversely related to tubular reabsorption. It is calculated by dividing the ratio of urinary-plasma (U/P) concentration of the solute by the U/P creatinine



Effect of indomethacin therapy on urinary excretion of Na and K.

ratio, and it is expressed as the percent of filtered solute excreted:

$$F_E \text{ of solute} = (U/P \text{ solute})/(U/P \text{ creatinine} \times 100)$$

Normal values for sodium are 0.5 to 1.0; for calcium, 0.5 to 1.0; for inorganic phosphate, 2 to 20; and for potassium, 10 to 20.

RESULTS

Clinical and laboratory findings are provided in the Table and Figure. During the control period, the data for both patients are consistent with the diagnosis of Bartter's syndrome. The serum potassium level was at the lower limits of normal in patient 1 (3.5 and 3.7 mEq/L), whereas patient 2 had persistent hypokalemia (serum potassium level of 3.1 and 3.2 mEq/L). The serum chloride level was low in patient 1. Both patients had elevated levels of urinary aldosterone excretion and of plasma renin activity. Serum PTH concentration was normal in patient 2.

In both patients, the rate of urinary excretion of sodium exceeded sodium intake during most of the control period while they were losing weight. At the end of the control period, the F_Es of sodium and inorganic phosphate were within normal limits: 0.53 and 2.41 in patient 1, and 1.01 and 18.4 in patient 2. The F_Es of calcium and potassium were higher than normal at the end of the control period in patient 1 (3.36 and 68.5); in patient 2, the F_E of calcium was 3.80, determined on the first day of the study, and the F_E of potassium was 26.90 on the last control day.

The day after indomethacin therapy was started, both patients gained weight (0.6 kg in patient 1 and 0.7 kg in patient 2). The increase in weight was maintained during the next four days without blood pressure changes. Patient 1 had a decrease in urinary output from 1,120 mL/24 hr to 515 mL/24 hr during the first day of indomethacin therapy. However, the urinary output returned to control values by the end of the trial. The serum sodium level remained unchanged after administration of indomethacin, whereas the serum potassium level increased and the blood pH decreased slightly, as did plasma base excess.

In both patients, sodium intake exceeded the rate of urinary sodium excretion during the indomethacin trial, and there were decreases in the F_Es of sodium, inorganic phosphate, calcium, and potassium. The maximal decrease of the F_E was found the day of the highest serum potassium concentration (second day of indomethacin therapy for patient 1 and fourth day of therapy for patient 2). In patient 1, the F_Es of sodium, calcium, and potassium had returned to or exceeded the control levels by the end of the therapeutic trial, with a concomitant decrease in the serum potassium concentration although still higher than control levels. Furthermore, despite the initial decrease in the F_E of potassium, her urinary potassium value exceeded the oral intake throughout the trial. At the end

Laboratory Data								
	Day of Study							
	Patient 1				Patient 2			
	1	4	6	8	1	4	6	8
Serum sodium, mEq/L	136	138	138	137	137	140	143	140
Serum potassium, mEq/L	3.5	3.7	4.6	3.9	3.1	3.2	3.9	4.3
Serum chloride, mEq/L	93	91	109	101	98	100	101	103
Venous blood pH	...	7.43	...	7.40	...	7.48	...	7.38
Plasma base excess, mEq/L	...	+4.3	...	−1.9	...	+6.3	...	+4.9
Plasma renin activity (normal, 0.75-3.00 ng/mL/hr)	26.0	...	...	4.8	13.3	...	...	2.2
Urinary aldosterone (normal, 4.0-13.0 μg/24 hr)	22.0	...	...	16.0	17.5	...	...	13.3
Creatinine clearance, mL/min/1.73 mL	67.4	...	...	50.4	18.8	...	...	24.3
Urinary fractional excretion of								
Phosphate	ND*	2.41	0.47	0.34	20.32	18.4	14.4	11.7
Calcium	ND	3.36	2.7	3.60	3.80	ND	3.00	1.41
Sodium	0.78	0.53	0.14	0.61	0.85	1.01	0.77	0.33
Potassium	110.00	68.5	42.53	94.40	29.20	26.90	27.79	22.08
Serum parathyroid hormone (normal < 250 pg/mL)	ND	...	...	206	<61	...	...	251

*ND indicates not done.

of the trial, there was a substantial reduction in plasma renin activity and urinary aldosterone excretion. At the same time, serum PTH levels remained within normal limits.

COMMENT

Patients with Bartter's syndrome have findings that are compatible with overstimulation of the renin angiotensin and the prostaglandin synthetase systems. Elevated levels of serum[7] and urinary prostaglandin E_2[4,6,7] have been reported in this condition. Proliferation of the medullary interstitial cells thought to produce prostaglandins[10,11] has been described.[3-5] The increase in plasma renin concentration, the rate of aldosterone excretion, and the hyperplasia of the juxtaglomerular apparatus are essential characteristics of Bartter's syndrome.[1] Furthermore, in these patients, a close correlation has been found between the concentration of urinary prostaglandin, the level of renin secretion and the rate of urinary aldosterone excretion.[4,6,7]

Patients with Bartter's syndrome have a decreased extracellular volume[2] and total exchangeable body sodium.[2] Since prostaglandin E_2 has been demonstrated to be natriuretic,[12] it has been postulated that the increase in prostaglandin would cause a primary renal salt wasting defect leading to sodium depletion with secondary activation of the renin angiotensin system resulting in hyperaldosteronism.[2]

Studies of renal tubular function in patients with Bartter's syndrome have shown decreased proximal[13,14] or loop of Henle[14-17] reabsorption of filtrate. The tubular reabsorptive defect can be partially or totally compensated for by an increase of the distal tubular reabsorption. Thus, most patients with this syndrome do not have obligatory salt loss because the increase in aldosterone secretion compensates for the tubular reabsorptive defect by augmenting the distal reabsorption of sodium.[18,19] However, this increases the urinary potassium loss by stimulating the sodium-potassium exchange at the distal tubule.

In our patients, the administration of indomethacin resulted in weight gain without blood pressure change, in sodium retention, and in an increase in the serum potassium concentration and improvement in the metabolic alkalosis. At the end of the trial, there was a decrease in the plasma renin concentration and the rate of urinary aldosterone excretion. These responses to indomethacin are consistent with the theory of increased prostaglandin production as a factor in the pathogenesis of Bartter's syndrome.

During indomethacin therapy, both our patients had an increase in tubular reabsorption of sodium and inorganic phosphate. Inorganic phosphate can be reabsorbed either at the proximal or distal segment of the nephron.[20] The proximal reabsorption is linked to sodium reabsorption and follows two mechanisms (PTH dependent and PTH independent).[20] The distal reabsorption is important only in the absence of PTH.[21] During indomethacin therapy, patient 1 had a normal PTH level, while the PTH level increased in patient 2. This suggests an increase in proximal tubular reabsorption of sodium and inorganic phosphate after prostaglandin inhibition, linked to the PTH-independent reabsorptive mechanism.

The decrease in the F_E of sodium seen in patient 1, before indomethacin therapy was begun, represents an adaptation to the reduced sodium intake. However, the further decrease in the F_E of sodium observed on the second day of indomethacin therapy cannot be attributed to this adaptive mechanism since it was well beyond expected levels. A 50% reduction of sodium intake, as in this case, would lead to a 50% reduction of the F_E. The F_E of sodium decreased from 0.78 to 0.14, representing an 80% reduction.

The increase in sodium reabsorption was maximal on the first day of therapy for patient 1 and on the fourth day for patient 2. However, although the sodium intake for patient 1 continued to exceed the urinary output throughout the trial, her F_E of sodium was approaching control levels on the fourth day of therapy. Probably, the

patient was in the process of achieving a new state of equilibrium based on an expanded extracellular volume. The volume expansion would decrease the proximal as well as distal sodium tubular reabsorption.[22] However, the increase in distal delivery of sodium in the presence of a still-activated renin aldosterone system may account for the increased rate of potassium excretion noted in patient 1 after the first day of indomethacin therapy by augmenting the sodium-potassium exchange at the distal tubule.

The serum potassium level increased in patient 1 despite the fact that the rate of urinary excretion of potassium exceeded the oral intake during indomethacin therapy. This increase in the serum potassium level was associated with sodium retention that would increase the sodium content of the RBC because of the known defect of the RBC membrane sodium-potassium adenosine triphosphatase in Bartter's syndrome.[23,24] The resultant displacement of intracellular potassium could then account for the increase in extracellular concentration of the cation.

Patient 1 had higher pretherapy and posttherapy renin levels than patient 2, and the metabolic indices for patient 1 improved less after indomethacin therapy. The higher renin levels may have reflected greater prostaglandin concentration[4,6,7] and, hence, less impact of indomethacin therapy on prostaglandin production.

The primary event leading to the increase in prostaglandin production in Bartter's syndrome is unknown although hypokalemia has been considered as the etiologic factor.[25] Prostaglandin E_2 levels are elevated in dogs depleted of potassium by hemodialysis.[26] However, the animals also had an increase in intravascular volume and serum sodium concentration. These findings are opposite to what occurs in patients with Bartter's syndrome.[1,2] In the canine experiment, renal prostaglandin production could have been secondary to the expanded vascular volume or the increase in serum sodium concentration.[27]

Increased prostaglandin synthesis as a basic pathogenic mechanism in Bartter's syndrome is an attractive hypothesis. Our patients seemed to benefit from the prostaglandin synthetase inhibitor therapy. Of all available drugs, indomethacin seems to be the most effective.[7] A wide range of opinion exists as to the severity and practical importance of untoward reactions to indomethacin. Nausea, vomiting, abdominal pain, headaches, and dizziness are dose dependent, and the reported frequency has varied greatly. However, because fatalities and morbidity secondary to peptic ulceration and hepatic toxic effects have been reported,[28] this mode of therapy should be reserved for patients whose metabolic abnormalities cannot be controlled by potassium supplements and antialdosterone agents alone.

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Allen W. Root, MD, performed the parathyroid hormone radioimmunoassay. Arlan L. Rosenbloom, MD, reviewed the manuscript. The Clinical Research Center staff from the W. Shands Teaching Hospital, Gainesville, Fla, provided technical assistance.

Nonproprietary Name and Trademark of Drug

Triamterene—*Dyrenium*.

References

1. Bartter FC, Pronove P, Gill JR Jr, et al: Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis: A new syndrome. *Am J Med* 33:811-828, 1962.

2. Fichman MP, Telfer N, Zia P, et al: Role of prostaglandins in the pathogenesis of Bartter's syndrome. *Am J Med* 60:785-798, 1976.

3. Verberckmoes R, Damme B, vanClement J, et al: Bartter's syndrome with hyperplasia of renal medullary cells: Successful treatment with indomethacin. *Kidney Int* 9:302-307, 1976.

4. Gill JR Jr, Frölich JC, Bowden RE, et al: Bartter's syndrome: A disorder characterized by urinary prostaglandins and a dependence of hyperreninemia on prostaglandin synthesis. *Am J Med* 61:43-51, 1976.

5. Donker HAM, DeJong PE, Statiu S, et al: Indomethacin in Bartter's syndrome: Does this syndrome represent a state of hyperprostaglandinism? *Nephron* 19:200-213, 1977.

6. Bowen RE, Gill JR Jr, Radfar N, et al: Prostaglandin synthetase inhibitors in Bartter's syndrome: Effect on immunoreactive prostaglandin E excretion. *JAMA* 239:117-122, 1978.

7. Norby L, Flamenbaum W, Letz R, et al: Prostaglandin and aspirin therapy in Bartter's syndrome. *Lancet* 2:604-606, 1976.

8. Katz FH, Bortz AI: Treatment of Bartter's syndrome with naproxen. *N Engl J Med* 299:100, 1978.

9. Watt BK, Merrill AL: Composition of foods, in *Agriculture Handbook No. 8*. US Dept of Agriculture, 1963.

10. Muirhead EE, Germain G, Leach BE, et al: Production of renomedullary prostaglandins by renomedullary interstitial cells grown in tissue culture. *Circ Res* 31(suppl 2):161-171, 1972.

11. Janszen FH, Nugteren DH: Histochemical localization of prostaglandins synthetase. *Histochem J* 27:159-164, 1971.

12. Dunn MJ, Hood VL: Prostaglandins and the kidney. *Am J Physiol* 233:F169-F184, 1977.

13. Tomko DJ, Yeh BPY, Falls WF: Bartter's syndrome: A study of a 50-year-old man with evidence for a defect in proximal tubular sodium reabsorption and comments on therapy. *Am J Med* 61:111-117, 1976.

14. Bartter FC, Delea CS, Kawasaki T, et al: The adrenal cortex and the kidney. *Kidney Int* 6:272-280, 1974.

15. Bartter FC: The syndrome of juxtaglomerular hyperplasia with aldosteronism: Hypokalemic alkalosis and normal blood pressure. *Birth Defects* 10:104-108, 1974.

16. Chaimovitz C, Levi J, Better OS, et al: Studies on the site of renal salt loss in patients with Bartter's syndrome. *Pediatr Res* 7:89-94, 1973.

17. Gill JR Jr, Bartter FC, Taylor AA, et al: Impaired tubular chloride reabsorptions as a proximal cause of Bartter's syndrome, abstracted. *Clin Res* 25:526a, 1977.

18. Solomon RJ, Brown RS: Bartter's syndrome: New insights into pathogenesis and treatment. *Am J Med* 59:575-583, 1975.

19. Bryan GT, MacCardle RC, Bartter FC: Hyperaldosteronism, hyperplasia of the juxtaglomerular complex, normal blood pressure, and dwarfism: Report of a case. *Pediatrics* 37:43-50, 1966.

20. Wen SF: Micropuncture studies of phosphate transport in the proximal tubule of the dog: The relationship to sodium reabsorption. *J Clin Invest* 53:143-153, 1974.

21. Pastoriza-Muñoz E, Clinders RE, Lassiter WE, et al: Effect of parathyroid hormone on phosphate reabsorption in rat distal convolution. *Am J Physiol* 235:F321-F330, 1978.

22. Dirks JH, Seely JF, Levy M: Control of extracellular fluid volume and the pathophysiology of edema formation, in Brenner BM and Rector FC (eds): *The Kidney*. Philadelphia, WB Saunders Co, 1976, pp 495-552.

23. Gardner JD, Simopoulos AP, Lapey A, et al: Altered membrane sodium transport in Bartter's syndrome. *J Clin Invest* 51:1565-1571, 1972.

24. Haljamae H, Enger E, Sigstrom L: Cellular potassium transport and ATPase activity in Bartter's syndrome. *Scand J Clin Lab Invest* 35:53-58, 1975.

25. Bartter FC, Gill JR Jr, Frolich JC: Bartter's syndrome. *Adv Nephrol* 7:191-198, 1977.

26. Galvez OJ, Bay WH, Roberts BW, et al: The hemodynamic effects of potassium deficiency in the dog. *Circ Res* 14:11-16, 1977.

27. Dusing R, Melder B, Kramer HJ: Prostaglandins and renal function in acute extracellular volume expansion. *Prostaglandins* 12:3-10, 1976.

28. Brewer EJ Jr: Proceedings of the conference on the rheumatic diseases of childhood: VI. Therapy of the rheumatic diseases of childhood: Nonsteroidal anti-inflammatory agents. *Arthritis Rheum* 29:513-525, 1977.

A Syndrome of Infantile CNS Degeneration

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• **We describe six patients from five families, who have a syndrome that, to our knowledge, has not been previously reported. The syndrome is characterized by growth failure, ophthalmoplegia, optic atrophy, choreoathetosis, areflexia, hypotonia, dysmorphic facies, and severe mental and motor retardation. Some of the children also had microcephaly and seizures. The clinical course is remarkably uniform and slowly progressive. The abnormalities first noted are delayed psychomotor development and poor weight gain, and the others all develop within the first three years of life. The syndrome seems to be hereditary. Extensive laboratory investigation has not yielded an etiology. Until pathologic material is available, the disorder remains a syndrome and the diagnosis is established by the unique combination of neurological abnormalities.**

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We have had the opportunity to study six children with a previously unrecognized syndrome. Other additional cases, not examined by us, are also thought to have a similar disorder. We believe it is a hereditary disorder that is remarkably similar in manifestation and course.

REPORT OF CASES EXAMINED BY US

CASE 1.—The proposita was born at a full-term pregnancy to a gravida 2, para 1 who experienced mild nausea and vomiting in the second trimester. The parents are unrelated. The patient was related to those in cases 2 and 8 (see Fig 1). The patient was healthy at birth, but substantial delay in development was evident at age 3 months. When examined at age 4 months, she had poor control of her head, inability to roll over, hypotonia, and absent muscle stretch reflexes. The patient was not seen again until age 17 years when she was admitted to the hospital for generalized tonic-clonic seizures. At that time, she required total nursing care, and she had no intelligible speech. The patient could not walk, talk, sit without support, or feed herself. She was less than the third percentile for height, weight, and head circumference. Examination disclosed a severely retarded girl with optic atrophy bilaterally, external ophthalmoplegia, ptosis, hypotonia, absent stretch reflexes, choreoathetosis, and facial dysmorphism. Extensive laboratory studies, which were also performed in cases 3 and 6, included the following: complete blood cell count; serum electrolyte; liver function; serum magnesium; serum calcium and phosphate; serum creatinine; serum creatine phosphokinase; serum VDRL; chromosome (with banding); urine test for amino acids; serum amino acids chromatogram; thyroid function; adrenal function (hydrocortisone, adrenocorticotropic hormone-stimulation); edrophonium chloride (Tensilon); urine thiamine pyrophosphate adenosine triphosphate transferase inhibitor; immunoglobulin electrophoresis; lipoprotein electrophoresis; urine arylsulfatase; CSF for glucose, protein, cells, and IgG; serum ceruloplasmin; serum copper; urinary copper; routine urinalysis; ECG; computerized axial tomography of head; pneumoencephalogram; electromyogram (EMG); nerve conduction; muscle biopsy specimen; sural nerve biopsy specimen; and EEG. These studies disclosed no abnormalities. Her seizures are controlled by phenytoin sodium. There were several distant relatives with similar facial features, abnormal movements, and retardation, who died in infancy. Medical records of these individuals could not be obtained.

CASE 2.—The patient was born after an uncomplicated pregnancy, labor, and delivery to a 45-year-old gravida 5, para 4. The parents were unrelated. The patient is distantly related to those in cases 1 and 8

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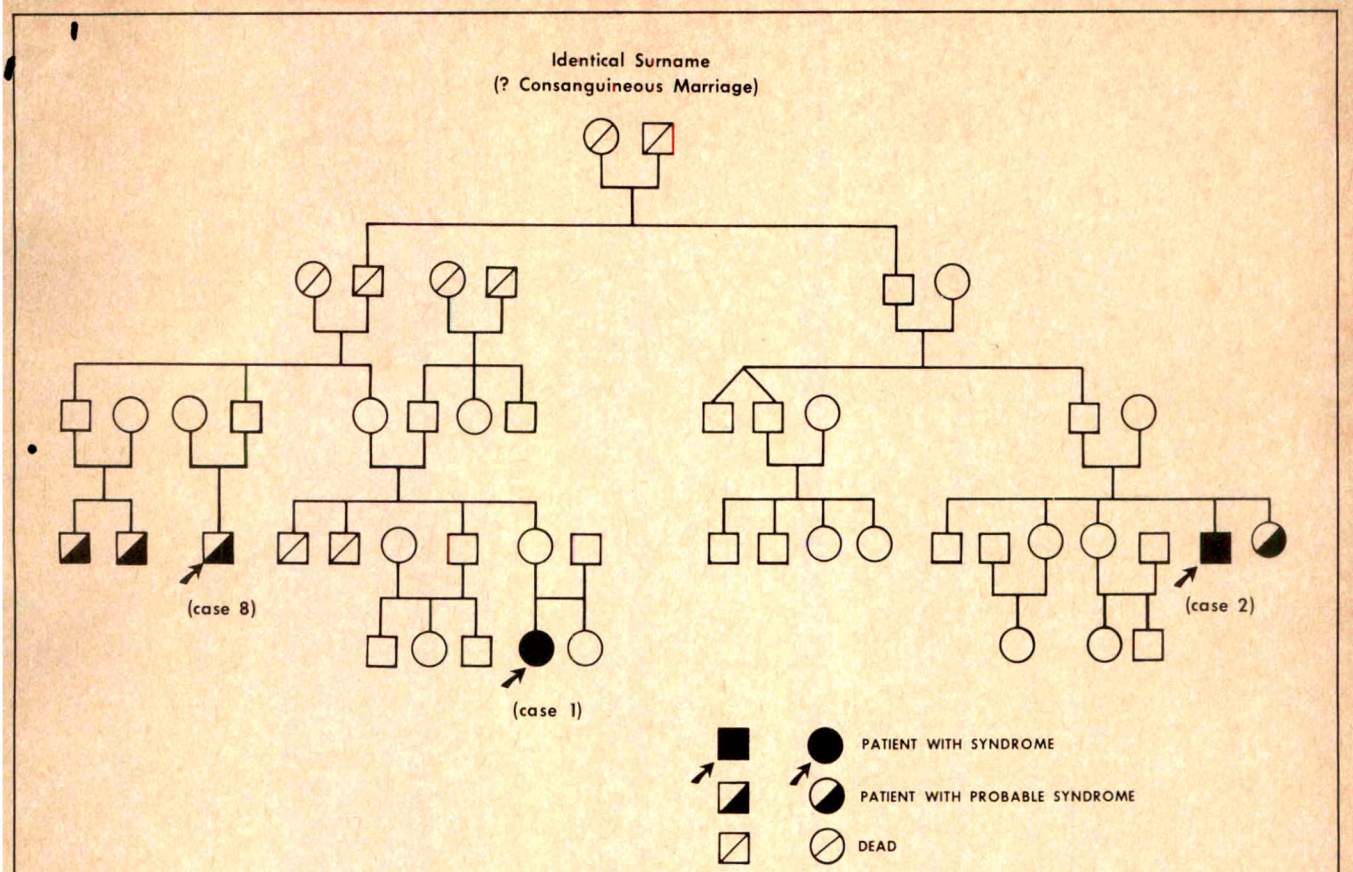

Fig 1.—Pedigree for cases 1, 2, and 8.

(see Fig 1). Because of failure to support the head and decreased muscle tone, the patient was admitted to the hospital at age 6 months for evaluation. Examination revealed normal extraocular movements, normal optic fundi, notably decreased muscle tone, areflexia, and developmental delay. Choreoathetosis was evident. The patient was seen again at age 12 years. At that time, he could not speak intelligibly, he was less than the third percentile for height and weight, and he could not walk. He required total nursing care, including feeding. There were facial dysmorphism, mild microcephaly, complete external ophthalmoplegia, ptosis, severe optic atrophy, hypotonia, areflexia, and almost continuous choreoathetosis.

Case 3.—The patient was born at a full-term, normal pregnancy, labor, and delivery to a 17-year-old primigravida who was uncertain of the father's identity. The patient was the niece of case 7. The neonatal period was unremarkable. At age 3 months, the patient had some control of her head and could roll over. However, during the next two years, she had little progression in development. She was admitted to the University of Virginia Medical Center, Charlottesville, at age 3½ years. She was unable to walk and had no intelligible speech. She was neither toilet trained nor able to feed herself, and she required total care. She was less than the third percentile for height and weight. Development was at a six-month level. There were microcephaly and mild facial dysmorphism, continuous choreoathetosis throughout waking periods, and advanced bilateral optic atrophy with sluggishly reactive pupils. She was severely hypotonic, with "frog leg" posturing of the lower extremities. During the next two years, she continued to display substantial delay in development and had major motor seizures that were easily controlled with phenytoin. She was reevaluated at age 6 years (Fig 2). Now there was total ophthalmoplegia with no movement of the eyes spontaneously or with caloric testing. As in case 1, the extensive laboratory investigations indicated no etiology for her disease.

Case 4.—This female infant was born to a gravida 3, para 2 who was not related to her husband. The pregnancy, labor, and delivery were uneventful. Developmental delay was evident during the first six months of life. The patient was examined again at age 6 years. At that time, height, weight, and head circumference were less than the third percentile. There were complete external ophthalmoplegia, ptosis, optic atrophy, mildly dysmorphic facies, hypotonia, areflexia, choreoathetosis, and severe motor and mental retardation. She could not sit, stand, or walk, and she had no intelligible speech. Since then, the patient's condition has changed little, and she requires total care (Fig 3). According to the father, there were "distant kin" with similar disorders. However, they had all died and medical records were not available.

Case 5.—This patient was born to an 18-year-old gravida 1, para 0 who denied difficulties during the pregnancy, labor, or delivery. The parents were unrelated. The immediate newborn period was normal. The child was evaluated at age 2 months because of poor head control. Hypotonia and diminished muscle stretch reflexes were found. At age 8 months, the child was admitted to the hospital for diagnostic appraisal. The child had little head control and a weak grasp, but she could roll over. She was hypotonic, with diminished stretch reflexes and choreoathetosis. She was again seen at age 6 years. She could not

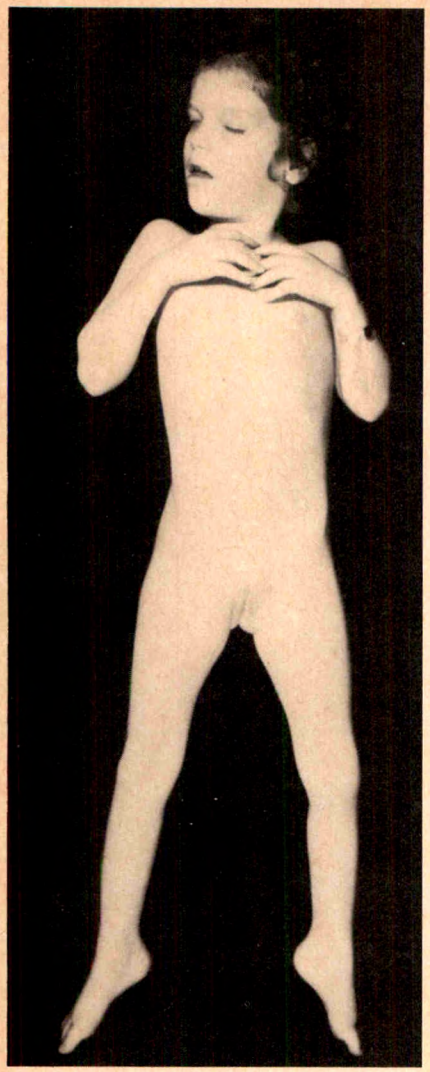

Fig 2.—Case 3, age 6 years. Note dysmorphic facies.

Fig 3.—Case 4, age 9 years. Note ptosis, dysmorphic facies, eye position.

Fig 4.—Case 6, age 19 years. Note ptosis, dysmorphic facies, eye position.

walk or speak, and she was less than the third percentile for height, weight, and head circumference. On examination, she demonstrated choreoathetosis, hypotonia, areflexia, severe mental retardation, optic atrophy, ophthalmoplegia, and mildly dysmorphic facies. She now requires total nursing care.

CASE 6.—The patient was born at a full-term pregnancy to a healthy 28-year-old gravida 2, para 1, abortus 0. The parents were unrelated. However, the maternal grandparents were said to be distant relatives. The labor and delivery were unremarkable, and the infant was regarded as normal. Early development was delayed. She was never able to walk or speak, she never became toilet trained, and she has required total nursing care. At age 6 years, she was found to have severe hypotonia, choreoathetosis, areflexia, and optic atrophy. She was less than the third percentile for height and weight. At age 16 years, she had a generalized convulsive disorder. Examination at age 19 years disclosed microcephaly, dysmorphic facies, bilateral optic atrophy, choreoathetosis, external ophthalmoplegia, ptosis, hypotonia, and absent stretch reflexes (Fig 4). As in cases 1 and 3, the extensive laboratory investigations showed no abnormalities. She continues to have occasional seizures, and she has been receiving maintenance levels of phenytoin and phenobarbital sodium. During the past six months, there has been further deterioration, with increasing difficulty in swallowing.

MEDICAL RECORDS OF CASES NOT EXAMINED BY US

CASE 7.—This patient was the maternal uncle of case 3. The patient was born at a full-term, normal pregnancy, labor, and delivery to a 23-year-old gravida 1, para 0 who was the second cousin of her husband. The patient was believed to be normal for the first several months, and then psychomotor development slowed. At age 10 months, he was admitted to the University of Virginia Medical Center. He was less than the third percentile for height and weight. He did not vocalize and had poor head control. He had microcephaly, optic atrophy, and ptosis, and he was unable to deviate his eyes to the left. Hypotonia with diminished stretch reflexes was present. He was described as having aimless movements of his arms and fingers. The patient contracted pneumonia at age 12 months and died at another institution. Postmortem examination was not obtained.

CASE 8.—This male infant was born to a 30-year-old gravida 6, para 5 who had the same maiden name as her husband and who was thought to be distantly related to him. The pregnancy, labor, and delivery were normal. The patient was related to those in cases 1 and 2 (see Fig 1). The child did not gain head control, meaningful speech, or the ability to sit or walk. At age 4 months, he had choreoathetosis of all extremities. At age 2 years, he was admitted to the hospital for pertussis. He was less than the third percentile for height and weight. He was noted to have continuous choreoathetosis of his arms and legs. Eye movements and optic fundi were not described. However, several examiners noted poorly reactive pupils. The child died of pneumonia. At postmortem examination, the child had evidence of diffuse bilateral pneumonia. The brain seemed normally developed, without any gross abnormalities. There was some meningeal congestion, and on microscopic examination, atrophy of the cortex and cerebellum was noted.

RESULTS

The Table summarizes the remarkably similar histories and signs that we have found in these eight unfortunate children. The malady seems to start early in infancy after an uneventful pregnancy, labor, and delivery. Early developmental delay is soon evident, with all being severely retarded and none being able to walk, speak intelligibly, or care for bodily

Clinical Findings in Syndrome

	Case No.							
	1	2	3	4	5	6	7	8*
Age, yr, mo	21	11	6	9	12	19	1†	2, 6†
Sex	F	M	F	F	F	F	M	M
Birth weight, kg	3.18	3.16	3.84	3.32	3.58	3.63	3.41	3.50
Developmental delay, age at onset, mo	<3	<3	≈6	<3	<3	<6	<6	<3
Examination findings‡								
Hypotonia	+	+	+	+	+	+	+	+
Optic atrophy	+	+	+	+	+	+	+	?
External ophthalmoplegia	+	+	+	+	+	+	+	?
Choreoathetosis	+	+	+	+	+	+	+	+
Mental deficiency	+	+	+	+	+	+	+	+
Areflexia	+	+	+	+	+	+	+	+
Seizures	+	+	+	—	+	+	—	—
Dysmorphic facies	+	+	Mild	+	Mild	+	?	?
Afflicted family members (by history)	+	+	+	+	—	—	+	+
Height and weight, percentile	<3rd	<3rd	<3rd	<3rd	<3rd	<3rd	<3rd	<3rd
Head circumference, cm (percentile)	52 (<3rd)	51 (20th)	49.5 (30th)	49 (<3rd)	50 (<3rd)	52 (<3rd)	46 (50th)	?

*Not examined by authors.
†Deceased.
‡+ indicates present; —, absent.

needs. Eye movements were normal initially with ophthalmoplegia beginning after age 3 years in all children except patient 7, who was found to have ophthalmoplegia at age 10 months. The ophthalmoplegia is complete, with no reflex movements. Optic atrophy seems to be a late finding, with the earliest detection being at 10 months, again in case 7. Unfortunately, the exact time of appearance of optic atrophy is difficult to estimate because of infrequent examinations in most of these children. Dysmorphic facies were present to a certain degree in all the patients examined by us, with the characteristic features of a wide nasal bridge, small mandible, and prominent maxilla. Figures 2 and 3 (cases 3 and 4) show patients with mild facial dysmorphism whereas Fig 4 (case 6) shows a patient with a severely dysmorphic face. All of our patients, in addition, had choreoathetosis, growth failure, and hypotonia early in the course. Microcephaly occurred in four patients and, when present, was mild. Seizures of various severity occurred in five. The seizures developed late in the course of the disease and tended to be generalized tonic-clonic seizures and, thus far, have been easily controllable.

The movement disorder occurs within the first year. It is bilateral, involving both the upper and lower extremities and disappearing with sleep. There does not seem to be any worsening of the movement disorder with age. One patient (case 6) was given a trial dose of a carbidopa-levodopa mixture, with no improvement in the choreoathetosis.

Several observations suggest that the disorder is inherited in an autosomal recessive pattern. Two of the patients examined by us (cases 1 and 2) and one other child not examined by us (case 8) were distantly related (Fig 1), and in several other families, there was a history of similarly affected children although this could be documented in only one additional family (cases 3 and 7). Although the families could not all be linked directly, the geneology of each patient included an identical surname. Consanguinity was frequent (all the family pedigrees are available on request from the authors).

Laboratory investigations were not helpful in determining the etiology of the disorder in our patients. Diagnostic studies done are listed in the report of case 1. Three patients (cases 1, 3, and 6) were studied extensively and had received all of the aforementioned tests except the muscle and nerve biopsy specimens, which were performed in case 1 only.

The disorder seems to be slowly progressive. The older patients in the series (ages 19 and 21 years) have changed little in the past six years. None of the patients examined by the authors have died, and brain tissue, therefore, has not been available. One patient, who was not seen by the authors (case 8), had only microscopic evidence of cortical and cerebellar atrophy at the time of death. Since a funduscopic examination was not done and eye movements were not described, we are unsure of whether this patient had the syndrome.

COMMENT

In the differential diagnosis, there are many syndromes that have some of the findings of the patients described. A brief review of syndromes that may be confused with our cases will be presented.

Seitelberger[1] in 1952 reported a previously undescribed syndrome that was characterized by onset before the second year of life, progressive psychomotor deterioration, hyperkinetic movements, hypotonia, limb and cranial nerve palsies, and optic atrophy. There is considerable controversy in the literature as to whether this disease is a variation of Hallervorden-Spatz disease or a separate disease, described by some authors as infantile neuroaxonal dystrophy.[2-6] The patients described in this report differ

from those with the varieties of Hallervorden-Spatz disease and infantile neuroaxonal dystrophy, primarily by the notable ophthalmoplegia.

Pelizaeus-Merzbacher disease has many of the characteristics of this syndrome.[7,8] The syndrome occurs in male subjects who are afflicted with a slowly progressive form of cerebral diplegia with the onset during infancy of nystagmus, poor head control, microcephaly, optic atrophy, spasticity, and growth failure. The syndrome is slowly progressive. Unlike our children, choreoathetosis and ophthalmoplegia are not consistent features in the Pelizaeus-Merzbacher syndrome.

Two other disorders that are similar to our syndrome include Krabbe's disease and Bassen-Kornzweig disease. Krabbe's disease is manifested by retardation of motor development, spasticity, seizures, optic atrophy, and the pathologic finding of globoid cells in the brain with a deficiency of galactocerebroside β-galactosidase.[9,10] Bassen-Kornzweig disease is characterized by a betalipoproteinemia, hypocholesterolemia, fat malabsorption, acanthocytosis, ataxia, chorea, nystagmus, weakness, muscle atrophy, peripheral neuropathy, and retinitis pigmentosa.[11] In neither of these syndromes is ophthalmoplegia a component. Multiple syndromes occur with ophthalmoplegia.[12] However, none bear an overall resemblance to the patients described.

On a clinical basis, our syndrome anatomically involves the cerebrum diffusely, with particular involvement of the optic nerves and basal ganglia. The hypotonia is probably on a central basis in view of the normal nerve conductions, EMG, and nerve and muscle biopsy specimens. Cerebellar involvement is difficult to assess because of the severe hypotonia, ophthalmoplegia, and choreoathetosis. The anatomical localization of the ophthalmoplegia remains unclear. As emphasized by Berenberg et al[13] and Rowland,[14] the disorder may reside in the ocular muscles, neuromuscular junction, cranial nerve nucleus, or supranuclear connections. Since pathologic specimens are not yet available, we cannot say definitely where the lesion is located. Until the time that pathologic material becomes available, the disorder remains a syndrome characterized by a unique combination of neurological abnormalities beginning during childhood.

References

1. Seitelberger F: Eine unbekannte Form von infantiler lipoidspeicher-Kkankheit des Gehirns, in *Proceedings of the First International Congress of Neuropathology*. Rome, Rosenberg & Sellier, 1952, vol 3, pp 332-333.
2. Wigboldus JM, Bruyn GW: Hallervorden-Spatz disease, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology. Diseases of the Basal Ganglia*, vol 6. Amsterdam, North-Holland Publishing Co, 1968, pp 604-631.
3. Cowen D, Olmstead EV: Infantile neuroaxonal dystrophy. *J Neuropathol Exp Neurol* 22:175-230, 1963.
4. Crome L, Weller SDV: Infantile neuroaxonal dystrophy. *Arch Dis Child* 40:502-507, 1965.
5. Huttenlocher PR, Gilles FH: Infantile neuroaxonal dystrophy. *Neurology* 17:1174-1184, 1967.
6. Gilman S, Barrett RE: Hallervorden-Spatz disease and infantile neuroaxonal dystrophy. *J Neurol Sci* 19:189-205, 1973.
7. Zeman W, Demeyer W, Falls HF: Pelizaeus-Merzbacher disease. *J Neuropathol* 23:334-354, 1964.
8. Tyler HR: Pelizaeus-Merzbacher disease: A clinical study. *Arch Neurol Psychiatry* 80:162-169, 1957.
9. Hagberg B: The clinical diagnosis of Krabbe's infantile leukodystrophy. *Acta Paediatr Scand* 52:213, 1963.
10. D'Agostino AN, Sayre GP, Hayles AB: Krabbe's disease. *Arch Neurol* 8:82-96, 1962.
11. Bassen FA, Kornzweig AL: Malformation of the erythrocytes in a case of typical retinitis pigmentosa. *Blood* 3:381-387, 1950.
12. Drachman DA: Ophthalmoplegia plus: A classification of the disorders associated with external ophthalmoplegia, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology. System Disorders and Atrophies*, vol 22, pt 2. Amsterdam, North-Holland Publishing Co, 1975, pp 203-216.
13. Berenberg RA, Pellock JM, DiMauro J, et al: Lumping or splitting? 'Ophthalmoplegia-Plus' or Kearns-Sayre Syndrome? *Ann Neurol* 1:37-54, 1977.
14. Rowland LP: Progressive external ophthalmoplegia, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology. System Disorders and Atrophies*, vol 22, pt 2. Amsterdam, North-Holland Publishing Co, 1975, pp 177-202.

Heart Failure in Cystic Fibrosis

Treatment and Prognosis of Cor Pulmonale With Failure of the Right Side of the Heart

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• **Failure of the right side of the heart with cardiac dilation and fluid retention occurred in 55 of 170 patients who died of cystic fibrosis; six patients survive. All had severe hypoxia, but 24% had normal $Paco_2$. Cardiac catheterization showed high mean pulmonary artery pressure and resistance. Pulmonary artery wedge pressure was greater than 12 mm Hg in 40% of the patients. Mean survival was eight months. Male survival was significantly better than female survival. Digitalis treatment was of no clear benefit. Tolazoline hydrochloride was also ineffective. Recent medical advances have not substantially affected prognosis.**

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Chronic alveolar hypoxia is largely responsible for the pulmonary hypertension[1,2] and resultant right-sided heart disease (cor pulmonale) that occur in the course of a variety of chronic pulmonary diseases.[2] Ultimately, overt right-sided heart failure with cardiac dilation and fluid retention may occur, and this seems to accelerate the deterioration of the patient's condition. This has been an increasingly common event in patients with cystic fibrosis[3-6] as increasing numbers of persons with this disease survive to young adulthood and later.[3,7] The recognition and treatment of this complication has received increased attention recently, and routine medical therapy including salt restriction and diuretics have generally been accepted as effective. The use of digitalis is more controversial,[8] and the more recently advocated vasodilator, tolazoline hydrochloride,[9] has not been adequately investigated.

We present here our experience with overt right-sided heart failure complicating cystic fibrosis. A total of 61 patients including 30 for whom cardiac catheterization data are available are described. The data suggest that the prognosis for this complication remains grim despite the continued use of salt restriction, the addition of more potent diuretic agents, and the use of digitalis and tolazoline.

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PATIENTS AND METHODS

The charts and chest roentgenograms of all patients with cystic fibrosis who have been seen at this center were reviewed. Cystic fibrosis was diagnosed by an abnormal sweat test in addition to either typical pulmonary or digestive symptoms or a family history of the disease.

The following criteria were used for the diagnosis of overt right-sided heart failure: (1) a 1.1-cm or greater increase in the size of the cardiac silhouette on sequential, standard posteroanterior chest roentgenograms during a period not exceeding six months; and (2) evidence of fluid retention (ie, a tender, enlarged liver and/or peripheral edema and/or ascites). Weight gain alone was not considered sufficient to establish fluid retention. Only patients who survived longer than two weeks after these initial criteria were met are included.

The clinical status of the patients, cardiac catheterization data, ECG data, pulmonary function data, and arterial blood gas determinations at the onset of overt right-sided heart failure were analyzed. The subsequent course of the patients' conditions with respect to treatment, additional complications, and survival are reported.

Patients undergoing cardiac catheterization received no sedation or other medication prior to the procedure. Pressure measurements were made using standard fluid-filled catheters and a physiologic pressure transducer and were recorded on a physiologic recorder. The zero level for pressure measurements was the midchest. Cardiac output was measured by a cardiogreen dilution technique[10] in 28 patients and by the Fick principle[11] in two patients.

Vectorcardiograms were obtained using the Frank system.[12] Echocardiograms were

recorded with an ultrasonoscope interfaced with a multichannel physiological recorder. Right and left ventricular dimensions were recorded from a standard position along the left sternal border. Measurement of right and left ventricles were made in end-diastole at the onset of the QRS complex. When aortic and pulmonic cusps could be recorded echographically, systolic time intervals were measured.[13]

Pulmonary function tests were performed by standard spirometric and plethysmographic techniques.[14-16] Blood gas analyses were performed by the clinical laboratory. Where appropriate, Student's *t* test for unpaired variables was used for statistical analyses.

RESULTS

Clinical Status

A total of 61 (8.3%) of the 728 patients seen at this center during a 20-year period had overt right-sided heart failure secondary to cystic fibrosis. The clinical status of the patients at onset of right-sided heart failure is summarized in Table 1. Only six of the 61 patients did not have liver tenderness and enlargement, whereas 22 (36%) did not have peripheral edema. Abnormal weight gain was absent in 38 patients; many patients, in fact, had lost weight since the time of their previous examination. Five patients had the typical murmur of tricuspid insufficiency develop either simultaneously with or shortly after the onset of cardiac dilation and fluid retention.

Data Analysis

Pulmonary function testing showed a consistent abnormality in the ratio of the residual volume to total lung capacity (RV/TLC), indicating severe obstructive disease. All patients had a value of 0.60 or greater (range, 0.60 to 0.85; mean, 0.70). Other pulmonary function results, although generally extremely abnormal, were less consistent. Vital capacity, for example, ranged from 21% to 68% of the predicted value for height, and the forced expiratory volume at one second (FEV_1) ranged from 17% to 74% of the vital capacity.

Arterial blood gas measurements showed consistent and severe hypoxemia (Pao_2 ranged from 18 to 49 mm Hg; mean, 35 mm Hg); but carbon dioxide tension was somewhat more

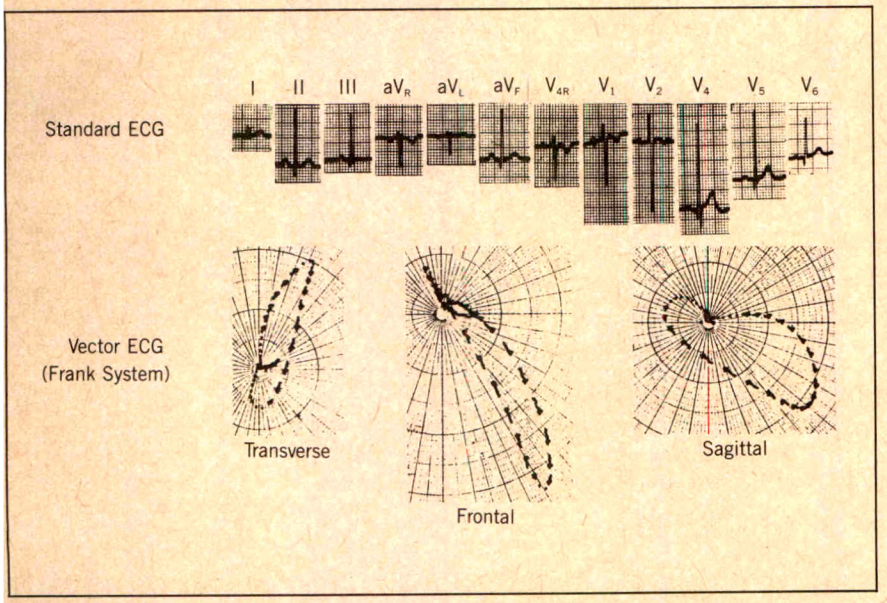
Table 1.—Clinical Findings of Patients With Cystic Fibrosis Who Had Secondary Cardiac Dilation and Fluid Retention*

Patient No./ Sex/Age, yr, mo	Tender Hepato-megaly	Edema	Weight Gain	Pao_2, mm Hg	$Paco_2$, mm Hg	Vital Capacity	RV/TLC	Survival, yr, mo
1/F/3, 1	+	–	+	35	51	. . .	. . .	0, 4
2/F/4, 5	+	–	–	38	73	. . .	. . .	0, 1
3/M/4, 10	+	+	–	. . .	. . .	. . .	. . .	0, 1
4/F/7, 4	+	–	–	28	45	43	.73	0, 4
5/F/7, 4	–	+	+	36	55	65	.61	0, 4
6/M/9, 7	+	–	–	. . .	. . .	33	.79	0, 2
7/F/9, 9	+	+	–	. . .	. . .	34	.76	0, 3
8/M/10, 3	+	+	+	. . .	. . .	57	.70	1, 7
9/F/10, 6	+	+	–	27	58	22	.85	2, 4
10/F/10, 6	+	+	–	45	50	38	.65	0, 1
11/M/11, 3	+	+	+	32	56	54	.62	0, 8
12/F/11, 8	+	–	–	28	50	44	.69	0, 3
13/M/11, 8	–	+	+	40	45	38	.69	1, 11
14/F/11, 11	+	+	–	24	68	30	.68	0, 1
15/F/12, 0	+	+	–	27	50	30	.71	0, 8
16/M/12, 2	+	–	–	43	64	56	.62	0, 1
17/M/12, 7	+	+	–	34	51	38	.64	0, 4
18/F/12, 8	+	–	+	44	50	47	.60	0, 6
19/M/13, 0	+	–	–	. . .	. . .	. . .	. . .	0, 1
20/M/13, 6	+	+	–	. . .	. . .	. . .	. . .	0, 1
21/F/14, 2	+	–	–	45	46	38	.71	0, 1
22/F/15, 0	+	+	+	30	76	21	.75	2, 4
23/M/15, 2	+	–	–	. . .	. . .	. . .	. . .	0, 1
24/F/15, 4	+	–	–	25	34	33	.78	0, 8
25/M/15, 7	+	+	–	. . .	. . .	. . .	. . .	0, 1
26/F/15, 9	+	–	–	41	47	32	.74	0, 1
27/F/16, 4	+	+	+	23	53	28	.85	0, 4
28/F/16, 4	+	+	–	36	42	41	.70	0, 5
29/F/16, 11	+	+	+	45	50	30	.73	0, 6
30/M/17, 2	+	+	+	34	61	29	.76	0, 7
31/F/17, 6	+	+	–	27	56	38	.71	0, 1
32/M/17, 6	+	+	+	40	55	44	.67	0, 10†
33/F/17, 9	+	+	–	18	62	30	.76	0, 1
34/F/18, 2	+	+	–	33	70	38	.71	0, 8
35/M/18, 6	–	+	–	49	68	33	.63	0, 1
36/M/18, 11	+	–	–	27	61	39	.71	0, 3
37/F/19, 1	+	+	–	49	41	33	.60	1, 6
38/F/19, 3	+	+	+	19	58	61	.60	0, 3
39/F/19, 9	+	+	+	42	41	49	.63	0, 1
40/M/19, 9	+	–	–	28	63	32	.52	1, 4
41/F/19, 10	+	+	+	. . .	. . .	. . .	. . .	0, 1
42/F/19, 10	–	+	–	42	30	40	.74	0, 7
43/F/19, 11	+	–	–	35	55	27	.79	0, 5
44/F/20, 2	+	+	+	44	48	43	.69	0, 5
45/F/20, 4	+	+	+	29	52	39	.76	0, 3
46/M/20, 7	+	–	–	33	56	47	.68	5, 1
47/M/20, 11	+	–	–	26	54	33	.79	0, 1
48/F/21, 1	+	+	+	30	50	60	.70	0, 11
49/M/21, 9	+	+	+	48	41	68	.61	0, 3
50/F/21, 11	+	+	+	. . .	. . .	44	.77	0, 4
51/M/23, 8	+	+	+	45	45	59	.77	0, 2
52/F/24, 1	+	–	–	35	60	43	.69	1, 3†
53/F/24, 3	+	+	+	44	50	47	.60	0, 6

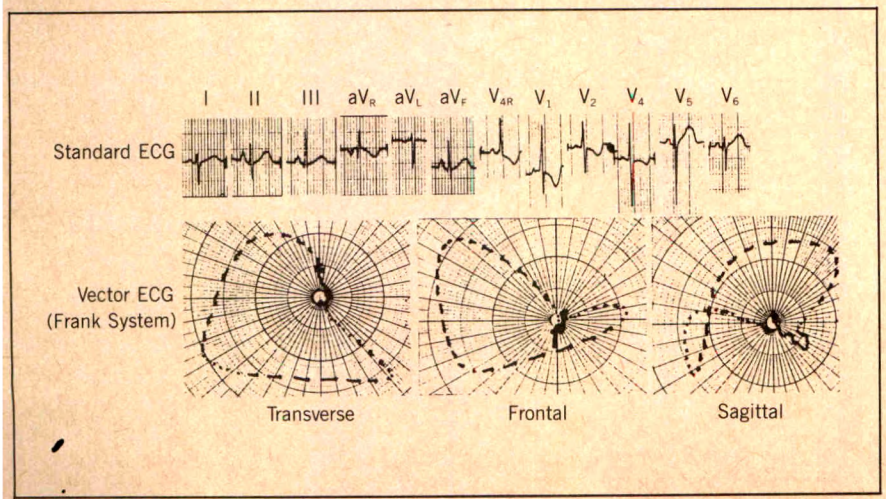
Table 1.—Clinical Findings of Patients With Cystic Fibrosis Who Had Secondary Cardiac Dilation and Fluid Retention (cont)*

Patient No./ Sex/Age, yr, mo	Tender Hepato-megaly	Edema	Weight Gain	Pao_2, mm Hg	$Paco_2$, mm Hg	Vital Capacity	RV/TLC	Survival, yr, mo
54/M/24, 4	+	+	+	26	64	36	.67	0, 4
55/M/25, 4	–	+	–	42	30	40	.68	0, 7
56/F/25, 7	+	+		42	60	25	.82	0, 4
57/M/26, 2	+	–		26	55	43	.62	0, 7†
58/M/26, 11	+	+		31	36	43	.60	3, 11†
59/M/28, 8	–	+		36	45	43	.74	1, 6
60/M/29, 4	+	+		31	61	43	.74	5, 3†
61/F/29, 6	+	+		34	70	41	.70	0, 10
Mean/16, 10	...	...		35	53	41	.70	0, 8

*Vital capacity is reported as percent of that predicted for height. RV indicates residual volume; TLC, total lung capacity; plus sign, present; minus sign, absent.
†Patient is alive as of Jan 1, 1979. Other patients have died.



Standard ECGs and vectorcardiograms for patients 40 (top) and 1 (bottom). Patient 40 has normal studies despite mean pulmonary artery pressure of 45 mm Hg and mean right atrial pressure of 10 mm Hg. Patient 1 has definite right ventricular hypertrophy despite generally milder, and presumably shorter duration, cardiovascular abnormality.



variable (range, 30 to 76 mm Hg; mean, 53 mm Hg), with 12 (24%) of the 51 patients for whom blood gas data were available having values less than 46 mm Hg.

Standard ECGs generally showed right ventricular hypertrophy (40 cases or 66%) and often showed right atrial hypertrophy (20 cases or 33%). Other findings included left ventricular hypertrophy, ST and T wave abnormalities, and low voltage. Six patients had completely normal ECGs. The top part of the Figure demonstrates this in one patient (patient 40), whose cardiac catheterization showed a mean pulmonary artery pressure of 45 mm Hg and a mean right atrial pressure of 10 mm Hg. His vectorcardiogram (Figure, top) was also normal. In other patients, vectorcardiographic abnormalities included right ventricular hypertrophy and abnormal posterior vector. The bottom part of the Figure illustrates both an extremely abnormal standard ECG and vectorcardiogram in a 3-year-old girl (patient 1), whose cardiac catheterization data was less abnormal than that of patient 40 (Figure, top). Echocardiographic measurements were generally more helpful in predicting ventricular size (by measurement) and in predicting diastolic pulmonary artery pressure (by assessment of the systolic time intervals).

Cardiac catheterization data for the 30 patients who had the procedure done are given in Table 2. There was considerable variation in the right atrial pressure (range, 1 to 29 mm Hg) at the onset of cardiac dilation; four patients (patients 12, 13, 46, 49) had normal or near-normal values. Although pulmonary artery pressure was invariably elevated, the range at onset of right-sided heart failure was considerable (28 to 70 mm Hg). The pulmonary artery wedge pressure was elevated (greater than 12 mm Hg) in 12 (40%) of the 30 patients.

Therapy

All patients were treated with low salt diet and diuretics. Diuretic therapy was intravenous (IV) initially (mercurial agents used with aminophylline or, more recently, ethacrynic acid, or furosemide). Many patients

Table 2.—Cardiac Catheterization Data for Patients With Secondary Cardiac Dilation and Fluid Retention

Patient No./Sex	Mean Right Atrial Pressure, mm Hg	Mean Pulmonary Artery Pressure, mm Hg	Mean Pulmonary Wedge Pressure, mm Hg	Mean Systemic Artery Pressure, mm Hg	Cardiac Index, L/min/sq m	Pulmonary Arterial Resistance, Resistance Units	Systemic Arterial Resistance, Resistance Units
1/F	5	35	8	82	6.3	4.3	12.2
9/F	20	60	8	59	3.3	15.8	11.8
10/M	22	36	14	85	5.2	4.2	12.1
12/F	4	53	8	82	5.8	7.8	13.4
13/M	1	29	8	75	3.7	5.7	20.0
14/F	26	70	12	85	3.7	15.7	15.9
15/F	8	41	8	55	3.0	11.0	15.7
21/F	13	60	14	90	7.9	5.8	9.7
22/F	8	42	18	95	4.4	5.5	19.8
24/F	8	46	8	55	7.6	5.0	6.2
27/F	25	35	8	75	3.8	7.1	13.2
28/F	15	70	13	90	4.4	13.0	17.0
31/F	14	65	12	95	6.9	7.7	11.7
33/F	12	60	13	75	5.8	8.1	10.9
34/F	10	68	10	75	4.4	13.2	14.8
38/F	21	65	15	80	2.3	21.7	25.7
40/M	10	45	5	80	6.7	6.0	10.4
45/F	15	50	15	100	5.8	6.0	14.7
46/M	5	28	10	83	5.2	3.5	15.0
47/M	8	60	10	96	5.5	9.1	16.0
48/F	10	60	10	90	5.6	8.9	14.3
49/M	4	36	6	85	4.4	6.8	18.4
51/M	8	49	16	82	2.3	14.3	32.2
54/M	29	65	16	65	2.7	18.1	13.3
56/F	13	40	15	80	4.7	5.3	14.3
57/M	16	55	26	90	2.4	12.1	30.8
58/M	16	62	18	91	2.5	17.6	30.0
59/M	15	50	10	90	4.5	8.9	16.7
60/M	16	58	9	85	5.1	9.6	13.5
61/F	28	50	. . .	93	3.1	. . .	21.0
Mean	14	51	12	82	4.6	9.5	16.4

received oral spironolactone or triamterene. Routine therapy for cystic fibrosis including pancreatic replacement at mealtime, supplemental vitamins, aerosols containing phenylephrine and/or isoproterenol hydrochloride, and oral antibiotics was continued. All patients also were treated intermittently with high-dose IV or intramuscular antibiotics. The use of digitalis was based mainly on the physician's preference rather than on any particular clinical finding. Tolazoline was used if a decrease in pulmonary arterial resistance with this agent had been demonstrated at cardiac catheterization or, for some patients who were not catheterized, if they had failed to respond to other measures for congestive heart failure.

Outcome

Survival data (Table 1) indicate a mean survival of eight months (median, four months; range, one month to 63 months) after onset of cardiac dilation and fluid retention; 39 (63%) of the 61 patients had died by six months, and 49 (80%) by 12 months. Three male patients have the longest survival (47 to 63 months); the longest survival by a female patient was 28 months. Male survival (mean, 12 months) was significantly longer ($P < .05$; unpaired t test) than that of female patients (mean, six months). There was no statistically significant difference in survival for patients during the five-year period from 1974 to 1979 (mean, 8.1 months) compared with those whose onset of cardiac dilation preceded 1974 (mean, 9.6 months).

Digitalis was used in 47 patients and their mean survival (8.0 months) was not significantly different from that of the 14 patients who did not receive digitalis (10.7 months). Tolazoline hydrochloride (1 mg/kg/dose, twice a day, intravenously) was given for at least one three-week course to 32 patients. Survival (mean, 9.1 months) was not significantly different from those patients who did not receive this treatment (mean, 8.3 months).

The five patients with the longest survival (greater than two years) were not, as a group, different from the remainder of the patients with regard to any of the clinical or laboratory findings reported here except that they were somewhat older. (Mean age of 20 years was compared with overall mean age of 16½ years for the remaining 56 patients.)

Autopsy data were available for 37 of the 51 patients who died in the hospital. All had right ventricular hypertrophy, and 19 had unequivocal right ventricular dilation; 13 had left ventricular dilation, and six had defi-

Table 3.—Incidence of Secondary Cardiac Dilation and Fluid Retention*

Age Range, yr	All Male Subjects			All Female Subjects			Total Seen			Died		
	Total No.	Cardiac Failure		Total No.	Cardiac Failure		Total No.	Cardiac Failure		Total No.	Cardiac Failure	
		No.	(%)		No.	(%)		No.	(%)		No.	(%)
0-4	389	1	0.3	339	2	0.6	728	3	0.4	25	3	12
5-9	370	1	0.3	327	2	0.6	697	3	0.4	30	3	10
10-14	270	7	2.5	246	8	2.8	516	15	2.9	42	15	35
15-19	173	8	4.6	171	14	8.1	344	22	6.3	42	21	50
20-24	105	5	4.7	84	6	7.1	189	11	5.8	20	7	35
≥ 25	31	5	16.1	15	2	13.3	46	7	15.2	11	6	55

*The decreasing numbers for successive age groups in the categories of patients seen at this center reflect losses owing to death and lack of follow-up for total number of 728 patients.

nite right atrial dilation. Three patients had focal myocarditis. All patients had extremely severe pulmonary involvement with bronchiolectasis and extensive destruction of pulmonary parenchyma. Eight patients (21%) had the typical biliary cirrhosis of cystic fibrosis. None of the patients had had clinical symptoms of hepatic disease.[17]

Of 170 patients who have died at this center, 55 (32%) are reported here to have had overt right-sided heart failure at least two weeks prior to death (six patients survive). The age-related and sex-related incidence rates among all patients seen at this center are presented in Table 3. There is a trend toward increasing incidence of overt right-sided heart failure with increasing age.

Two patients (patients 17, 37) required general anesthesia for surgical complications of cystic fibrosis after onset of overt right-sided heart failure. One (patient 37) had a pneumothorax develop nine months after cardiac dilation. Her condition failed to improve with supportive measures, and she finally had an open thoracotomy with total pleural abrasion and apical pleurectomy.[18] She is still alive 18 months after onset of right-sided heart failure and nine months after the thoracotomy. The other patient (patient 17) required operative intervention for recurrent (more than five episodes) intussusception and had a laparotomy when nonsurgical procedures were unable to effect reduction. Postoperatively, intussusception did not recur, but the patient died of respiratory failure two weeks later.

Virtually every patient was completely disabled after onset of overt right-sided heart failure although two (patients 52, 54) did return to full-time employment and continued to work for several months. Most patients required hospitalization frequently and for prolonged periods. On the average, after onset of cardiac dilation, 26% of the remainder of the patient's life was spent in the hospital.

COMMENT

Overt right-sided heart failure with cardiac dilation has become an increasingly common complication of the pulmonary lesion of cystic fibrosis as mean life expectancy for patients with this disease has been extended.[3] Our data (Table 3) suggest that this trend will continue. Whereas only 21% of our patients who died at 14 years or younger had this complication, 46% of those who died at 15 years or older did have overt right-sided heart failure at least two weeks prior to death. Similar results are obtained when the incidence of overt right-sided heart failure in patients who remain alive at various ages is examined (Table 3). Possibly, the older patients are exposed to more sustained and severe hypoxemia that permits the development of severe and unrelenting pulmonary hypertension.

At the onset of cardiac dilation, the great majority of patients had enlarged, tender livers, but only 64% had detectable peripheral edema. Ascites was rare. Interestingly, only 22 (38%) had demonstrable weight gain since their previous hospitalization or clinic visit. Many, in fact, had lost weight. The most probable reason for this is that the ongoing weight loss of chronic disease had exceeded the weight gain from fluid retention. In any case, however, the absence of weight gain should not be considered as evidence that a patient with cystic fibrosis does not have right-sided heart failure.

Arterial blood specimens, available for 51 patients, confirmed the relationship of right-sided heart failure to severe hypoxia.[1] All Pao_2 values were less than 50 mm Hg (mean, 34.8; SD, 8.3). Some patients were extremely hypoxemic, with 27 having values less than 35 mm Hg. Five patients were so well compensated to chronic hypoxemia that they were able to walk into the hospital with Pao_2 values ranging from 18 to 25 mm Hg. Hypercarbia was apparently of far less importance in that almost 25% of the patients had normal or near normal values.

Although severe hypoxemia was a constant finding, there was considerable variability in pressure and resistance data obtained at cardiac catheterization (Table 2). Some patients had normal right atrial pressures and cardiac outputs. These findings do not rule out congestive failure, which exists when cardiac output is unable to meet metabolic needs of the body. In addition, these tests were performed at rest; any additional activity might have changed the findings considerably. By contrast, however, other patients did not have overt heart failure develop until much more severe abnormality in the pulmonary circulation had developed. The reason for these individual differences is not clear.

Standard pulmonary function findings included a consistent and severely abnormal RV/TLC ratio. The vital capacity, although abnormal, did

not show as close a correlation with mean pulmonary artery pressure or with pulmonary vascular resistance as expected. For example, one patient (patient 48) with a vital capacity of 60% of that predicted had a mean pulmonary artery pressure of 60 mm Hg, whereas another (patient 56) with a vital capacity of 25% of that predicted had a mean pulmonary artery pressure of only 40 mm Hg.

Standard ECG and vectorcardiographic findings were not closely correlated with pulmonary vascular resistance or mean pulmonary artery pressure. Echocardiography, however, was useful if systolic time intervals could be obtained. In addition, the echocardiogram has been able to differentiate those patients with left ventricular dysfunction from those with "pure" right ventricular failure. This may prove important in the selection of patients for catheterization and in the determination of which studies should be performed.

The data confirm the grim prognosis for patients who have overt right-sided heart failure develop.[4-6] Mean survival was only eight months and has not been substantially affected by recent, more aggressive medical management. The survival for the past five years is not better than for the preceding 15 years. Similarly, digitalis does not seem to offer any substantial benefit to the majority of these patients, with survival rates in those treated (mean, eight months) similar to those not treated (mean, ten months).

Recently, tolazoline has been reported to lower mean pulmonary arterial resistance and pulmonary artery pressure.[9,19,20] Although initial results with clinical use seemed favorable,[19,20] we now report that, in this substantially larger group of patients, this drug does not seem to have any clear-cut effect on survival. There is little doubt, however, that short-term use of diuretics resulted in subjective improvement and we have shown previously[21] the effectiveness of IV diuretics for heart failure by measurements of right atrial pressure. All patients in this series received treatment with diuretics and low salt diet.

The somewhat better course in male patients is not easily explained but is consistent with the widely reported better prognosis for male subjects, both in individual centers[7] and from analysis of cooperative national statistics.[22] All three patients who survived longer than three years were male as was one patient reported elsewhere.

Our data suggest that future assessment of treatment measures for overt right-sided heart failure in cystic fibrosis including tolazoline, low-flow oxygen, prophylactic digitalis, or low salt diet must include appropriate control patients. Left ventricular unloaders would also seem to deserve a trial in selected patients. An effective approach to this complication is urgently needed, as demonstrated by our dismal survival statistics.

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Nonproprietary Names and Trademarks of Drugs

Ethacrynic acid–*Edecrin.*
Triamterene–*Dyrenium.*

References

1. Fishman AP: State of the art: Chronic cor pulmonale. *Am Rev Respir Dis* 114:775-794, 1976.
2. World Health Organization Expert Committee: Chronic cor pulmonale. *Circulation* 27:594-615, 1963.
3. Wood RE, Boat TF, Doershuk CF: State of the art: Cystic fibrosis. *Am Rev Respir Dis* 113:833-878, 1976.
4. Moss AF, Harper WH, Dooley RR, et al: Cor pulmonale in cystic fibrosis of the pancreas. *J Pediatr* 67:797-807, 1965.
5. Siassi B, Moss AJ, Dooley RR: Clinical recognition of cor pulmonale in cystic fibrosis. *J Pediatr* 78:794-805, 1971.
6. Moss AJ, Dooley RR, Mickey MR: Cystic fibrosis complicated by heart failure. *West J Med* 122:471-473, 1975.
7. Stern RC, Boat TF, Doershuk CF, et al: Course of cystic fibrosis in 95 patients. *J Pediatr* 89:406-411, 1976.
8. Green LH, Smith TW: The use of digitalis in patients with pulmonary disease. *Ann Intern Med* 87:459-465, 1977.
9. Kelminson LL, Cotton EK, Vogel JHK: The reversibility of pulmonary hypertension in patients with cystic fibrosis: Observations on the effects of tolazoline hydrochloride. *Pediatrics* 39:24-35, 1967.
10. Kinsman JM, Moore JW, Hamilton WF: Studies on circulation: I. Injection method: Physical and mathematical considerations. *Am J Physiol* 89:322-330, 1929.
11. Rudolph AM: *Congenital Diseases of the Heart.* Chicago, Year Book Medical Publishers, 1974.
12. Hugenholtz PG, Liebman J: The orthogonal vectorcardiogram in 100 normal children (Frank system). *Circulation* 26:891-901, 1962.
13. Hirschfeld S, Meyer R, Schwartz DC: Measurement of right and left systolic time intervals by echocardiography. *Circulation* 51:304-309, 1975.
14. Willmon TL, Behnke AR: Residual lung volume determinations by the methods of helium substitution and volume expansion. *Am J Physiol* 153:138-142, 1948.
15. Comroe JH Jr, Forster RE II, DuBois AB, et al: *The Lung: Clinical Physiology and Pulmonary Function Tests.* Chicago, Year Book Medical Publishers, 1962, pp 7-27.
16. Dubois AB, Botelho SY, Bedell GN, et al: A rapid plethysmographic method for measuring thoracic gas volume: A comparison with a nitrogen washout method for measuring function residual capacity in normal subjects. *J Clin Invest* 35:322-326, 1956.
17. Stern RC, Stevens DP, Boat TF, et al: Symptomatic hepatic disease in cystic fibrosis: Incidence, course and outcome of portal systemic shunting. *Gastroenterology* 70:645-649, 1976.
18. Stowe SM, Boat TF, Mendelsohn H, et al: Open thoracotomy for pneumothorax in cystic fibrosis. *Am Rev Respir Dis* 111:611-617, 1975.
19. Fisher BJ, Liebman J, Doershuk CF, et al: A pilot study evaluating the physiologic effects of priscoline on cor pulmonale in cystic fibrosis, in *Cystic Fibrosis Club Abstracts.* Atlanta, National Cystic Fibrosis Foundation, 1971, p 17.
20. Liebman J, Lucas RV, Moss A, et al: Cor pulmonale and related cardiovascular effects of cystic fibrosis, in Mangos JA, Talamo RC (eds): *Cystic Fibrosis: Projections into the Future.* New York, Stratton Intercontinental Medical Book Corp, 1976, pp 41-80.
21. Whitman V, Stern RC, Bellet P, et al: Studies on cor pulmonale in cystic fibrosis: I. Effect of diuresis. *Pediatrics* 55:83-85, 1974.
22. Warwick WJ, Pogue RE, Gerber HU, et al: Survival patterns in cystic fibrosis. *J Chronic Dis* 28:609-622, 1975.

Nonketotic Hyperglycinemia

Effects of Therapy With Strychnine

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• Nonketotic hyperglycinemia was diagnosed in identical twins with lethargy and respiratory failure in the neonatal period. Therapy with strychnine (0.32 mg/kg/day) resulted in great reductions in CSF and plasma glycine levels and improvement in muscle tone, respiration, and ability to suck. Myoclonic seizures were partially controlled by therapy with clonazepam. Higher dosages of strychnine (up to 2.0 mg/kg/day) were needed to counteract the increased lethargy following administration of clonazepam. At 5 months of age, the twins' developmental performance remained below the 1-month level despite adequate somatic growth. The twins died suddenly of status epilepticus at 6½ months of age.

(*Am J Dis Child* 134:273-275, 1980)

Nonketotic hyperglycinemia (NKH) is a rare, inherited disorder of glycine metabolism characterized by muscular hypotonia, myoclonic seizures, mental retardation, and early death.[1] Glycine levels in plasma may be elevated up to three times normal and large amounts of glycine are excreted in the urine. The poor prognosis in this disorder has been attributed to absence of both hepatic and cerebral glycine cleavage enzyme activity.[2] Defective oxidation of glycine to serine[3,4] results in glycine accumulation in CSF with levels 15 to 30 times normal and a glycine content two to four times normal in several brain regions.[2]

Previous therapeutic approaches with this disorder have included restriction of dietary glycine intake; administration of compounds potentially active in replenishing the pool of single carbon units; supply of the coenzyme precursor pyridoxine; and administration of glycine-binding agents.[5-9] Glycine levels in plasma were lowered in one patient who was treated with sodium benzoate and a ventriculoperitoneal shunt[9]; however, CSF glycine concentrations remained unchanged. None of these treatments have effectively prevented mental retardation, even when instituted in the neonatal period.[9]

Glycine is thought to act as an inhibitory neurotransmitter in the brain stem, in the spinal cord, and in some neurons in higher centers.[10-13] Strychnine has high affinity for glycine receptors[12-14] and therefore acts as a glycine antagonist. Gitzelman and others[15-17] have reported treatment of NKH with strychnine.

Therapy with strychnine was used for NKH in identical twin boys in whom the condition was diagnosed in the neonatal period. The effects of therapy with strychnine were followed with monitoring of serial plasma and CSF glycine levels. Changes in activity and development of the two infants were also evaluated.

REPORT OF CASES

One pair of twins (both male) were the product of a 40-week gestation in a 20-year-old, gravida 1, para 1, blood type O, Rh-positive mother. The prenatal course was unremarkable and fetal activity had been normal. An elective cesarean section was carried out at term for malpresentation in a twin gestation. Baby A weighed 2,550 g, was delivered from a transverse lie, and had Apgar scores of 7 and 9 at ages 1 and 5 minutes, respectively. Baby B weighed 2,650 g, was delivered by the breech, and had Apgar scores of 7 and 9 at ages 1 and 5 minutes, respectively. The placenta was monochorionic-diamniotic. Blood subgrouping showed that the twins were Rr, M−, N+, P+, L−, Duffy A−, S−. This, together with the placental findings, confirmed that the twins were identical. The family history showed no metabolic, neuromuscular, or CNS diseases. The infants were normal initially, but increasing lethargy was noted over the first three days of life. Eventually, both infants required gavage feeding and did not cry after circumcision. Some minor tremors of the limbs but no overt seizure activity was noted. The infants were referred to Women and Infants Hospital of Rhode Island, Providence.

On admission, the twins were flaccid and did not react to painful stimuli. Their vital

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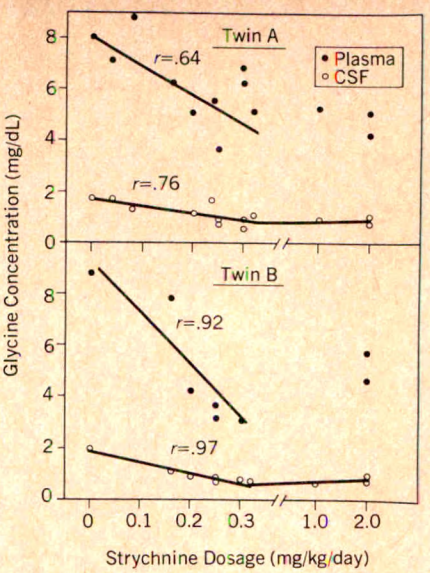
signs and measurements were as follows: twin A, temperature was 37.3 °C, pulse rate was 136 beats per minute, respirations were 36/min, weight was 2,435 g, head circumference was 33 cm, length was 49 cm; twin B, temperature was 36.3 °C, pulse rate was 150 beats per minute, respirations were 44/min, weight was 2,600 g, head circumference was 33 cm, length was 52 cm. Both twins were normocephalic with normal anterior fontanels. They did not open their eyes spontaneously; however, a normal red reflex was elicited and a doll's eye reflex was present. Rooting reflex was absent. Sucking and gag reflexes were poor. Moro's reflex was absent. No fasciculations were seen. Deep tendon reflexes were present; they were reduced in the upper extremities and hyperreflexic in the knees and ankles. Plantar reflexes were unresponsive. There were no external congenital anomalies, and the results of the remainder of the examination were normal. Within 48 hours of admission, progressive respiratory failure developed in both infants, requiring assisted ventilation.

Complete blood cell count and serum electrolyte, glucose, calcium, phosphorus, magnesium, bilirubin, protein, BUN, arterial pH, and blood gas levels were within normal limits. Results of lumbar puncture showed normal CSF.

Skull and chest roentgenogram, electromyogram, and muscle biopsy specimens were normal. Electroencephalogram showed a quiet sleep pattern with bursts of sharp wave activity that were thought to be paroxysmal in nature. There was no improvement in muscle tone with administration of edrophonium chloride (Tensilon). Urine, blood, and CSF organic acid, mucopolysaccharide, and amino acid levels were normal except for the glycine level, which was sharply elevated (Figure). Glycine was measured in serum and CSF using column chromatography on an amino acid analyzer. In the absence of acidosis, a diagnosis of NKH was made on the basis of markedly elevated glycine levels in both plasma and CSF (Figure).

Informed consent having been obtained from the parents, therapy with oral strychnine was instituted at a dosage of 0.04 mg/kg/day divided into six hourly doses. The dosage was increased every 48 hours until the twins were breathing well enough to be extubated. On the tenth day of therapy with strychnine, both infants had seizures and their strychnine dosage was reduced from 0.3 mg/kg/day to 0.2 mg/kg/day. However, it was necessary to increase the dosage again to 0.3 mg/kg/day and then to 0.32 mg/kg/day to facilitate sucking. The twins went home on day



Plasma and CSF glycine concentrations relative to the dosage of strychnine given to twins with nonketotic hyperglycinemia. Normal ranges for children 1.3 months old: Level of glycine in plasma, 0.79 to 1.67 mg/dL; level of glycine in CSF, 0.022 to 0.078 mg/dL.

34 of therapy with strychnine and required only occasional gavage feedings. Their weight at the time of discharge was 2,945 g and 3,190 g, respectively. They were seen daily by a visiting nurse and were seen weekly in our follow-up clinic.

Two weeks after discharge, the twins exhibited excessive myoclonic jerking. Their strychnine dosage was reduced to 0.25 mg/kg/day. However, two weeks later, the weight of each twin was reduced 500 g, increasing lethargy developed, respirations slowed to 20 and 24/min, respectively, and they were readmitted to the hospital. The strychnine dosage was increased stepwise to 1.0 mg/kg/day with a concomitant improvement in respiratory rate and resumption of sucking. Electroencephalograms showed a hypsarrhythmia pattern in both twins. Administration of clonazepam was begun at a dosage of 0.01 mg/kg/day and was increased slowly to 0.2 mg/kg/day. Myoclonic jerks became less prominent. However, the infants became more lethargic and did not suck as well while receiving clonazepam. The strychnine dosage was increased stepwise to 3.0 mg/kg/day with improved sucking and muscle tone. Generalized seizures developed in twin B at this dosage and so the strychnine dosage for both twins was reduced to 2.0 mg/kg/day. They were sent home receiving this dosage divided every four hours, the clonazepam being given before meals and the strychnine afterwards. Weight gain and head growth were maintained along the fifth percentile.

Neurologically, at 5 months of age, the infants had normal muscle tone, but with marked strabismus and occasional myoclonic jerks. Neither infant was able to focus his gaze because of strabismus. Both infants managed an occasional smile and they raised their heads infrequently; they functioned below the 1-month level.

COMMENT

Therapy with strychnine resulted in a fall in plasma and CSF glycine levels in these identical twin males with NKH, and a concomitant improvement was seen in the muscle tone and the level of consciousness (Figure). However, despite early diagnosis (18th day of life) and the use of increasing dosages of strychnine (up to 2.0 mg/kg/day), the developmental prognosis for the infants remained poor and the plasma and CSF glycine levels remained elevated within the range of mild NKH as recently reported by Frazier et al.[18] The toxic-therapeutic ratio of strychnine dosage seems to be narrow since at a dosage of 0.15 mg/kg/day, these infants were too lethargic to suck and at 3.0 mg/kg/day, generalized convulsions developed in twin B.

It is likely that the beneficial effect of strychnine on muscle tone and level of consciousness in NKH is due to the antagonism of excessive glycine-mediated postsynaptic inhibition.[10,13,19] However, the role of strychnine-glycine interactions in the underlying hypsarrhythmic seizure disorder in the twins and in other infants[15] is not clear. Strychnine and glycine bind to different sites at the glycine receptor, so that only part of the strychnine bound to nervous tissue membranes is displaced by glycine.[20] Strychnine also reduces the in vitro binding of β-alanine to synaptosome-enriched fractions of rat brain.[21] Hence, the effects of strychnine in vivo are probably not solely due to reduction of glycine-mediated postsynaptic inhibition.

Clonazepam, a derivative of medazepam (Benzodiazepine) hydrochloride, was useful in controlling excessive strychnine-induced myoclonic jerks associated with the hypsarrhythmic seizure disorder seen in these infants. It has been suggested that

benzodiazepines act on glycine receptors and thereby interfere with strychnine binding[22]; however, this mechanism remains controversial.[23,24]

Although strychnine produced a remarkable improvement in hypotonia, respiratory drive, and sucking activity in the twins, which was correlated with concomitant reductions in plasma and CSF glycine levels, their plasma and CSF glycine levels remained elevated and their neurologic functions did not become normal. Moreover, their strychnine dosage had to be adjusted frequently and the drug may have exacerbated their underlying hypsarrhythmic seizure disorder. However, the improvement in respiratory and feeding functions did allow us to discharge the patients and the parents were able to care for them at home.

The twins died suddenly of status epilepticus within 15 minutes of each other at 6½ months of age. They had been admitted to the hospital prior to further metabolic studies. We suspected a medication error. However, concentrations of strychnine in the blood and urine of both twins measured at the time of autopsy were as follows: twin A, blood, 0.44 mg/dL, urine, 0.18 mg/dL; twin B, blood, 0.38 mg/dL, urine, 0.12 mg/dL.

These levels are within the toxic range but below the lethal range reported in adults.[25] There are no data for infants or children. Important autopsy findings were limited to the brain. Both cases showed microvacuolization of white matter and diffuse gliosis of the gray matter. One twin had hypoplasia of the corpus callosum and slight hydrocephalus. The cause of death may have been related to their medication or to an underlying seizure disorder. Results of developmental testing within one week of death showed that both twins were functioning below the 1-month level.

Mary Ann Ampola, MD, performed the glycine determinations.

Nonproprietary Name and Trademark of Drug

Clonazepam—*Clonopin.*

References

1. Nyhan WL: Nonketotic hyperglycinemia, In Nyhan WL (ed): *Heritable Disorders of Amino Acid Metabolism.* New York, John Wiley & Sons Inc, 1974, pp 308-315.
2. Perry TL, Urquhard N, MacLean J, et al: Nonketotic hyperglycinemia glycine accumulation due to absence of glycine cleavage in brain. *N Engl J Med* 292:1266-1273, 1975.
3. Ando T, Nyhan W, Geritsen T, et al: Metabolism of glycine in the nonketotic form of hyperglycinemia. *Pediatr Res* 2:254-263, 1968.
4. Baumgartner RE, Nyhan WL: Nonketotic hyperglycinemia. *J Pediatr* 75:1022-1030, 1969.
5. DeGroot CJ, Troelstra JA, Hommes FA: Nonketotic hyperglycinemia: An in vitro study of the glycine-serine conversion in liver of three patients and the effect of dietary methionine. *Pediatr Res* 4:238-243, 1970.
6. Koepp P, deGroot CJ, Gruttner R, et al: Clinical findings and therapeutic problems in nonketotic hyperglycinemia. *Helv Paediatr Acta* 28:459-465, 1973.
7. Spielberg SP, Lucky AW, Schulman JD, et al: Failure of leucovorin therapy in nonketotic hyperglycinemia. *J Pediatr* 89:681-682, 1976.
8. Trijbels JMF, Monnens LAH, van der Zee SPM, et al: A patient with nonketotic hyperglycinemia: Therapeutic approaches. *Pediatr Res* 8:598-605, 1974.
9. Krieger I, Winbaum ES, Eisenbrey AB: Cerebrospinal fluid glycine in nonketotic hyperglycinemia: Effect of treatment with sodium benzoate and ventricular shunt. *Metabolism* 26:517-524, 1977.
10. Aprison MH, Daly EC, Shank RP, et al: Neurochemical evidence for glycine as a transmitter and a model for its intrasynaptosomal compartmentation, in Berl S, Clarke DD, Schneider D (eds): *Metabolic Compartmentation and Neurotransmission.* New York, Plenum Press Inc, 1975, pp 37-48.
11. Roberts E, Hammerschlag R: Amino acid transmitters, in Seigel GS, Albers RW, Katzman R, et al (eds): *Basic Neurochemistry,* ed 2. Boston, Little Brown and Co, 1976, pp 131-168.
12. Ryall RW: Amino acid receptors in CNS: I. GABA and glycine in spinal cord, in Iversen LL, Iversen SD, Snyder SH (eds): *Handbook of Psychopharmacology* ed 4. New York, Plenum Press Inc, 1975, pp 83-122.
13. Synder SH: The glycine synaptic receptor in the mammalian central nervous system. *Br J Pharmacol* 53:473-484, 1975.
14. Curtis DR, Duggan AW, Johnston GAR: The specificity of strychnine as a glycine antagonist in the mammalian spinal cord. *Exp Brain Res* 12:547-565, 1971.
15. Gitzelman R, Steinman B, Otten A, et al: Nonketotic hyperglycinemia treated with strychnine, a glycine receptor antagonist. *Helv Paediatr Acta* 32:517-525, 1977.
16. Garcia-Castro JM, Levy HL, Shik VE: Nonketotic hyperglycinemia treated with strychnine, abstracted. *Pediatr Res* 12:506, 1978.
17. Ch'ien LT, Chance P, Arneson D, et al: Glycine encephalopathy. *N Engl J Med* 298:687, 1978.
18. Frazier DM, Summer GK, Chamberlin HR: Hyperglycinuria and hyperglycinemia in two siblings with mild developmental delays. *Am J Dis Child* 132:777-781, 1978.
19. Aprinson MH, Davidoff PA, Werman R: Glycine: Its metabolic and possible transmitter roles in nervous tissue. *Handb Neurochem* 3:381-397, 1970.
20. Young AB, Snyder SH: Strychnine binding in rat spinal cord membranes associated with the synaptic glycine receptor: Cooperactivity of glycine interactions. *Mol Pharmacol* 10:790-809, 1974.
21. Orensanz Munoz LM, DeFeudis FV, Fando JL: High-affinity binding of glycine and β-alanine to synaptosome-enriched fractions of rat CNS regions: Effects of strychnine. *Gen Pharmacol* 8:325-330, 1975.
22. Young AB, Zukin SR, Synder SH: Interaction of benzodiazepines with central nervous system glycine receptors: Possible mechanism of action. *Proc Natl Acad Sci USA* 71:2246-2250, 1974.
23. Curtis DR, Game CJA, Lodge D: Benzodiazepines and central glycine receptors. *Br J Pharmacol* 56:307-311, 1976.
24. Squires RF, Baestrup C: Benzodiazepine receptors in rat brain. *Nature* 226:732-734, 1977.
25. Baselt RC, Cravey RH: A compendium of toxic concentrations of toxicologically significant drugs in human biofluids. *J Analytic Toxicology* 1:81-103, 1977.

Renal Venous Thrombosis in Neonates

Initial and Follow-up Abnormalities

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• **Five neonates with renal venous thrombosis (RVT) were studied at the onset of the disease, and four have been followed up for from 24 to 32 months after the time of diagnosis. Reduced glomerular filtration (two of four cases) on follow-up occurred only in infants with bilateral abnormalities as shown by results of physical examination, urography, renal scan, and angiography. Results of contrast studies showed the similarity between resolved RVT and certain congenital renal abnormalities. Renal tubular defects (polyuria, acidosis, hyperkalemia) constituted the primary clinical abnormalities in one of the two infants with renal insufficiency. Although the prognosis of RVT after medical management has improved, the ultimate outcome is unknown; the possibility of unsuspected neonatal RVT should be considered during investigation of children with unilaterally or bilaterally small kidneys.**

(*Am J Dis Child* 134:276-279, 1980)

Renal venous thrombosis (RVT) is suspected in a patient, particularly a neonate, in whom hematuria and an enlarged kidney develop shortly after a period of asphyxia, shock, dehydration, or sepsis.[1-3] The suggestion has been made that RVT is a bilateral disease but with asymmetrical involvement, such that a minor lesion in the less-involved kidney might be overlooked.[4] The thrombosis commonly begins in the interlobular or arcuate veins of the kidney and less commonly in the main renal vein. The thrombosis may spread retrograde to involve the cortex or may extend inward to the main renal veins and the inferior vena cava. As the result of venous obstruction, infarction and hemorrhage occur and blood leaks into the interstitium and tubules, which may result in fibrosis.

A number of factors seem to be related to the pathogenesis of RVT. Dehydration has been implicated as the most common cause in infants and newborns.[4-6] The infants of diabetic mothers have an increased susceptibility to RVT[7,8] and children with congenital heart disease who have had angiographic studies are also susceptible to RVT.[4]

During a two-year period, we have cared for five neonates with RVT. The initial and subsequent evaluation and therapy of these patients are the subject of this report.

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PATIENTS

Initial Evaluation

One infant was born to a class B diabetic mother; the mothers of the other four infants were all in good health. All the neonates were male and three were preterm. Grunting and retraction developed in case 2 during the first hour of life and a chest roentgenogram showed a diffuse reticulogranular pattern and air bronchograms. Results of an initial blood determination showed acidemia and subsequent determinations showed hypoxemia and hypercapnea and continued acidemia. This patient required respiratory support for seven days. Case 4 was delivered by low forceps; after intubation, his condition improved immediately and he was extubated after ten minutes. Case 5 was also delivered by low forceps and there was abruptio placentae with an estimated maternal blood loss of 1,000 mL. Extubation was performed after four hours.

Cultures of blood, urine, and CSF were performed in three neonates (cases 2, 4, and 5) during the first few hours of life and therapy with ampicillin sodium and gentamicin sulfate was begun for treatment of possible sepsis. The antibiotic therapy was discontinued after 48 hours in all patients on receipt of negative culture reports. A seizure disorder developed in case 5 at six

hours of age and therapy with phenobarbital was begun.

Gross hematuria was detected during the first 48 hours of life in all patients except case 2, in whom microscopic hematuria developed two days and gross hematuria four days after birth (Table 1). Proteinuria was present in all patients and cases 4 and 5 had oliguria for a mean period of five days. The blood pressure was recorded in three infants during the acute state of the disease and was normal in all.

Enlarged kidneys were first noted at the onset of hematuria in three infants and within three days in the other two infants. Three infants (cases 1 to 3) had unilaterally and two (cases 4 and 5) had bilaterally enlarged kidneys (Table 1). At the time of initial evaluation, the serum creatinine level was increased in all patients and the BUN level was elevated in three patients (Table 2). The highest ratios of BUN level-creatinine level were 28 to 1.8, 28 to 1.9, 12 to 1.5, 44 to 5.7, and 26 to 6.7 mg/dL in cases 1 to 5, respectively. The two infants with bilateral RVT (cases 4 and 5) had serum potassium concentrations of 6.5 and 6.6 mEq/L, respectively, during the acute stages of the illness and case 5 had persistent hyperkalemia (6.1 to 6.7 mEq/L) throughout his first year of life.

Results of initial urographic and renal isotopic studies (Table 2) correlated with physical findings; unilaterally enlarged kidneys were nonfunctioning or abnormal and bilaterally enlarged kidneys were both abnormal. Results of inferior vena cavagraphy in the two cases studied were not diagnostic of RVT.

Case 5 showed severe anemia due to abruptio placentae and was given a blood transfusion shortly after birth. The peripheral blood smear from three infants (cases 2, 4, and 5) showed occasional fragmented RBCs and burr cells, and the platelet count was decreased in these same infants (< 100,000/cu mm). However, the levels of plasma fibrinogen and fibrin split products were normal.

Case 4 received therapy with heparin sodium during the period of oliguria (seven days). He initially received 100 units/kg of heparin sodium as a single dose followed by 25 units/kg/hr. The dosage of heparin sodium was adjusted every eight hours to maintain the partial thromboplastin time (PTT) between 2½ to three times normal. In spite of careful calculations, the PTT was usually either below or above the desired range.

Table 1.—Initial Renal Findings in Five Patients With Renal Venous Thrombosis

Case	Microscopic Hematuria/ Gross Hematuria, Age at Onset, Days	BUN, mg/dL	Creatinine, mg/dL	Renal Mass Detected (Day)
1	2/2	28	1.8	R (2)
2	2/4	28	1.9	L (5)
3	1/1	12	1.5	L (1)
4	2/2	32	2.8	R, L (2)
5	1/1	10	2.7	R, L (3)

Table 2.—Initial Anatomical Studies in Five Patients With Renal Venous Thrombosis

Case	Intravenous Urogram	Renal Scan	Inferior Vena Cavagram
1	R, no visualization L, bifid collecting system	R, no perfusion or concentration L, optimal perfusion and concentration	
2	R, normal visualization L, no visualization		Inferior vena cava patent R, washout absent L, washout absent
3	R, normal visualization L, no visualization	R, optimal perfusion and concentration L, no perfusion or concentration	
4	R, no visualization L, no visualization	R, no perfusion or concentration L, no perfusion or concentration	Inferior vena cava patent R, washout absent
5	R, minimal visualization L, minimal visualization	R, moderate perfusion and concentration L, minimal perfusion and concentration	

Table 3.—Follow-up Clinical and Laboratory Data

	Case			
	1	2	4	5
Age, mo	28	32	24	25
Height, percentile	10	3	3	50
Weight, percentile	75	25	3	25-50
Blood pressure, mm Hg	84/54	80/58	96/. . .	70/44
BUN, mg/dL	15	15	31	33
Serum creatinine, mg/dL	0.4	0.4	1.2	0.8

FOLLOW-UP STUDIES

Case 1.—At 38 months of age, this patient had normal renal function (Table 3). The results of radiographic studies, however, showed a small, shrunken right kidney and an enlarged left kidney (Fig 1). There was some evidence of delayed psychomotor development that was considered secondary to environmental deprivation.

Case 2.—This patient became slightly hypertensive by 4 months of age. At 17 months of age, an intravenous (IV) urogram showed a small shrunken left kidney (Fig 2) and a hypertrophied right kidney. Chest roentgenogram and ECG were normal. Results of selective renal vein renin assay showed elevated renin levels; the right side was 39.5 ng/mL/hr and the left side 30.3 ng/mL/hr (normal, 1.5 ng/mL/hr). By aortography, the left renal artery was detectable but smaller than the right renal artery (Fig 3). This patient received no antihypertensive therapy and his blood pressure has been normal for the past 12 months. Renal function at 32 months of age was normal (Table 3). His height was at the third percentile.

Case 3.—This patient has been lost to follow-up.

Case 4.—At 24 months of age, this patient had impaired renal function (Table 3) and was receiving sodium bicarbonate.

The latest anatomical studies were performed at 11 months of age. On IV urogram, the right kidney did not appear. Results of radioisotopic study showed reduced perfusion and concentration in both sides, with the right side more impaired than the left (Table 4).

CASE 5.—At 11 months of age, case 5 had appropriate height and weight, but renal function was impaired (Table 3). His therapy included sodium bicarbonate because of acidosis. An inferior vena cavagram performed at 2½ months of age was normal. There was bilateral "washout" of contrast at the level of the renal veins (Table 4). Intravenous urography at 2½ months of age showed no excretion of contrast medium from either kidney for up to three hours, but the renal scan was normal. When last seen at age 25 months, renal function was abnormal but growth and development were normal (Table 3). Neonatal seizure activity required continued therapy with phenobarbital and no seizures have occurred subsequently.

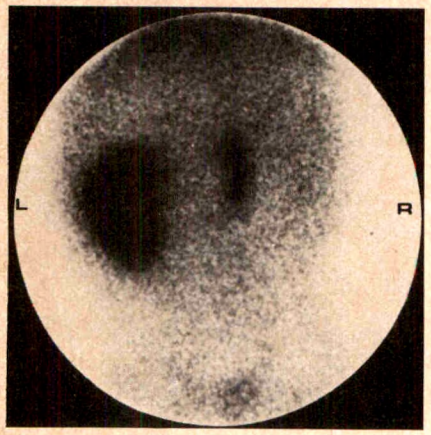
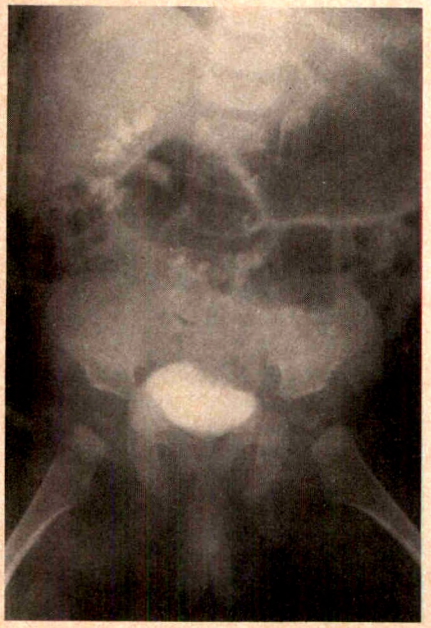


Fig 1.—Follow-up renal scan, case 1 at 16 months of age. Minimal concentration of radionuclide in small right kidney. Left kidney is enlarged and has normal concentration of isotope (Tc 99m diethylenetriamine penta-acetic acid).

Fig 2.—Intravenous urogram, case 2 at 7 months of age. Right kidney is larger than normal but left kidney is small and has decreased concentrations of contrast medium.



COMMENT

The natural history of RVT in infants has received considerably less attention than have the early diagnostic and therapeutic aspects of this disease. In the course of this study of five infants with RVT, a variety of physiological and roentgenographic abnormalities appeared in four infants after an observation period of from 24 to 32 months. The residual defects from neonatal RVT resembled those seen in other congenital and acquired lesions, which emphasizes the importance of careful evaluation and follow-up of infants with suspected neonatal RVT.

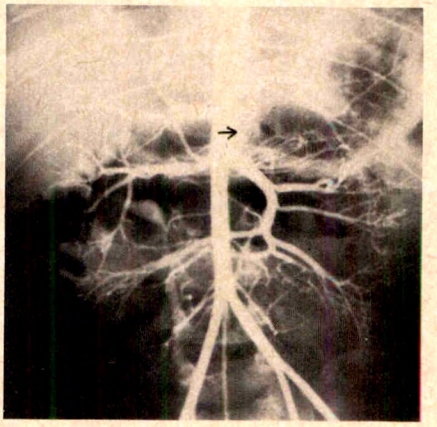


Fig 3.—Arteriogram, case 2 at 17 months of age. Left renal artery (arrow) is very small, but right renal artery is normal.

Only two infants, both having had bilateral RVT, had slight elevations of serum creatinine level at follow-up (creatinine levels, 0.8 and 1.2 mg/dL, respectively). These infants required bicarbonate replacement; one had polyuria as well as hyperkalemia during his first year of life (case 5). Although glomerular filtration was reduced in these two infants (as reflected by slightly elevated serum creatinine levels), interstitial and tubular damage seemed to be more important during the period of observation.

Hypertension is a feared consequence of neonatal RVT, yet the incidence of this complication was only 6/50 cases in one review.[5] The only patient in our series with hypertension (case 2) was not treated and the hypertension has disappeared. A small renal artery and a shrunken kidney with hypertrophy of the contralateral kidney were detected in case 2 and have been mentioned by other workers.[9] In the absence of prior clinical information, these radiographic abnormalities might otherwise suggest the presence of a congenitally dysplastic or "hypoplastic" single kidney.

Table 4.—Follow-up Anatomical Studies

Case	Intravenous Urogram (Age at Time of Study)	Renal Scan (Age at Time of Study)
1	R, small-minimal visualization L, large-normal visualization duplex system (28 mo)	R, reduced perfusion and concentration L, normal perfusion and concentration (28 mo)
2	R, large-normal visualization L, small-minimal visualization (7 mo)	R, normal perfusion and concentration L, reduced perfusion and concentration (7 mo)
3	R, large-normal visualization L, small-minimal visualization (3 mo)	
4	R, no visualization L, minimal visualization (11 mo)	R, reduced perfusion and concentration L, reduced perfusion and concentration (11 mo)
5	R, no visualization L, no visualization (2½ mo)	R, normal perfusion and concentration L, normal perfusion and concentration (2½ mo)

Consequently, we believe that detection of a small renal artery is not sufficient evidence of a congenital rather than acquired small kidney.

Radiographic IV urography, inferior vena cavagraphy, aortography, renal scan,[9] and ultrasonography are helpful in supporting the clinical diagnosis, but none of these procedures are definitive. The renal scan correlated well with the ultimate outcome in our series, and in view of its small amount of radiation exposure, it may be a particularly useful test for RVT. Evidence of RVT in the arterial phase of aortography includes stretching or bowing of the interlobular vessels and delayed transit time of the contrast medium.[10,11] In the urographic phase, whether the injection is made via umbilical catheter or through a peripheral vein, the kidneys are not demonstrable on the affected side in most patients with RVT.[4,11] We performed vena cavagraphy on only two cases and in each it was normal. The stream of unopacified blood from the renal vein may produce a radiolucent image (washout) in the inferior vena cava at the L1 to L2 level during vena cavagraphy. However, absence of washout is not specific for RVT, as it can also occur in some healthy persons[12] or in persons with any renal disorder in which there is a reduction in renal blood flow. Furthermore, failure to detect thrombosis of the inferior vena cava cannot eliminate the diagnosis of RVT due to the variability in the site of thrombosis.

Anemia, fragmented RBCs and burr cells, as well as thrombocytopenia, decreased serum fibrinogen, and increased fibrin degradation products have been reported in patients with RVT. These findings raise the probability of consumptive coagulopathy accompanied by RVT,[13] but the condition of the only patient in our series who received heparin has progressed to renal failure.

The emphasis of the management of the neonate with RVT should be placed on the maintenance of normal fluid and electrolyte balance.[4] Some patients may require peritoneal dialysis although this was not necessary in our series. Unilateral thrombectomy or nephrectomy during the acute stages is generally not advocated.[2,5,9] Since Stark[2] first noted survival of infants with RVT not subjected to nephrectomy, several reports have confirmed the safety of this nonsurgical approach.[9,14] Nephrectomy had previously been advocated to prevent (1) infection, now an infrequent complication, (2) hypertension, a serious problem usually after healing and renal atrophy occurs, and (3) extension of thrombosis, an apparently rare complication in neonatal RVT.[9] Furthermore, many instances of return of function in the damaged kidney are now documented. Subsequent nephrectomy for persistent hypertension may be required, however.[4,9] Thrombectomy for bilateral involvement has been successfully performed at some centers,[15] but the role of this procedure in RVT is presently unclear.

Christopher F. O'Connor and Brendan M. Fox referred their patients. Susan Maguda gave secretarial assistance.

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Gentamicin sulfate—*Garamycin.*

References

1. Kaufmann HJ: Renal vein thrombosis. *AMA J Dis Child* 95:377-384, 1958.
2. Stark H: Renal vein thrombosis in infancy: Recovery without nephrectomy. *Am J Dis Child* 108:430-435, 1964.
3. Fallon ML: Renal vein thrombosis in the newborn. *Arch Dis Child* 24:125-128, 1949.
4. Arneil GC, MacDonald AM, Murphy AV, et al: Renal venous thrombosis. *Clin Nephrol* 1:119-131, 1973.
5. Olson D: Renal vein thrombosis, in Lieberman E (ed): *Clinical Pediatric Nephrology*, ed 1. Philadelphia, JB Lippincott Company, 1976, pp 372-380.
6. McFarland JB: Renal vein thrombosis in children. *Q J Med* 34:269-290, 1965.
7. Takeuchi A, Benerschke K: Renal vein thrombosis of the newborn and its relation to maternal diabetes. *Biol Neonate* 3:237-256, 1961.
8. Avery ME, Oppenheimer EH, Gordon HH: Renal vein thrombosis in newborn infants to diabetic mothers. *N Engl J Med* 256:1134-1138, 1957.
9. McDonald P, Tarar R, Gilday D, et al: Some radiologic observations in renal vein thrombosis. *Am J Roentgenol Radium Ther Nucl Med* 120:368-388, 1974.
10. Chait A, Stoane L, Moskowitz H, et al: Renal vein thrombosis. *Radiology* 90:886-896, 1968.
11. Hipone FA, Crummy AB: The roentgen diagnosis of renal vein thrombosis. *Am J Roentgenol Radium Ther Nucl Med* 98:122-131, 1966.
12. Scanolon GT: The radiologic changes in renal vein thrombosis. *Radiology* 80:208-211, 1963.
13. Renfield ML, Draybill EN: Consumptive coagulopathy with renal vein thrombosis. *J Pediatr* 82:1054-1056, 1973.
14. Belman AB, Susmano DF, Burden JJ, et al: Nonoperative treatment of unilateral renal vein thrombosis in the newborn. *JAMA* 211:1165-1168, 1970.
15. Mauer SM, Fraley EE, Fish J, et al: Bilateral renal vein thrombosis in infancy: Report of a survivor following surgical intervention. *J Pediatr* 78:509-512, 1971.

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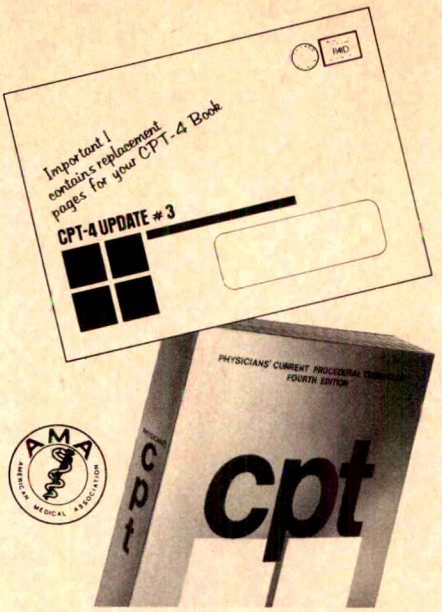

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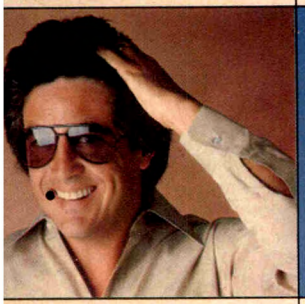			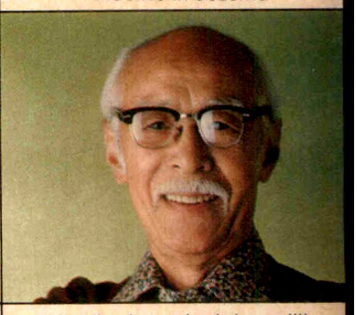
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		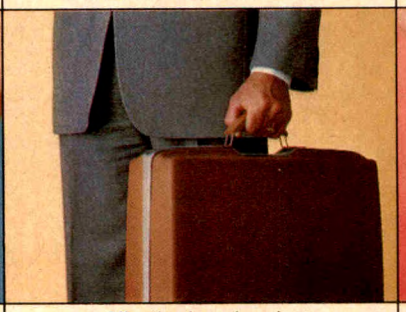	
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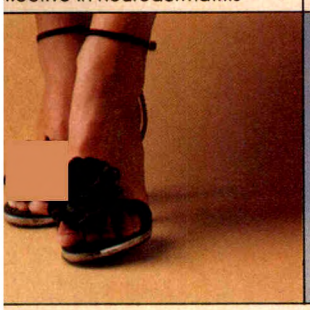			

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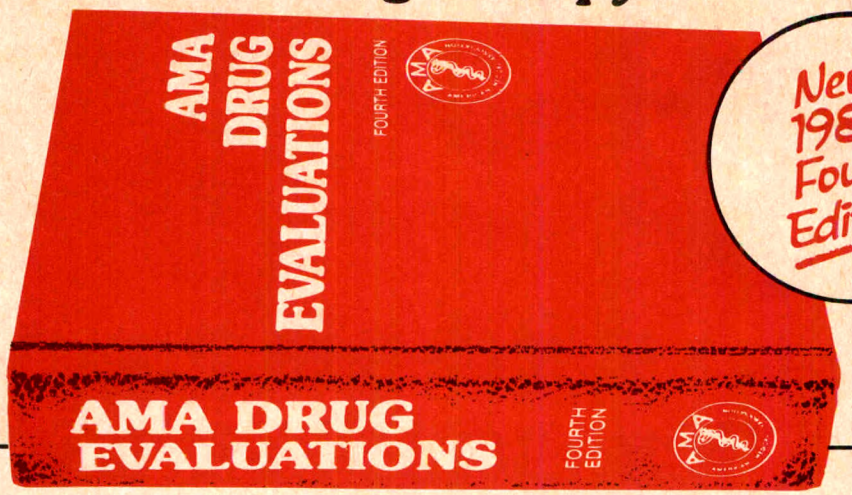

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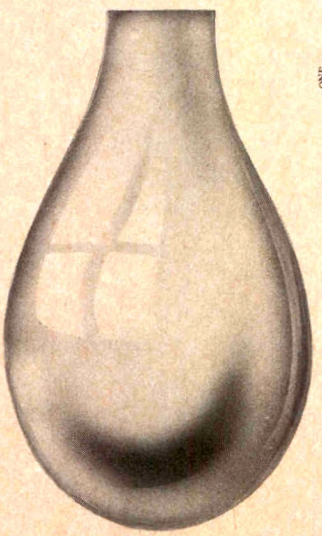

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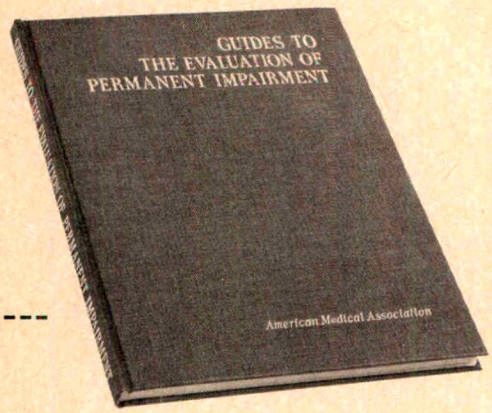

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Campomelic Dysplasia

Further Elucidation of a Distinct Entity

Bryan D. Hall, MD, Jürgen W. Spranger, MD

• Campomelic dysplasia is a distinct entity that should not be confused with other conditions associated with congenital bowing of the long bones. Evidence suggests that some affected males have female external genitalia, and vagina, uterus, and fallopian tubes. Examination of a newly reported sibling pair has increased support for autosomal recessive inheritance in campomelic dysplasia.

(*Am J Dis Child* 134:285-289, 1980)

The term "campomelic syndrome" or "campomelic dysplasia" (the latter is the preferred term[1]) was originally coined to describe a distinct entity.[2] Later, it was also applied to other disorders that share the feature of campomelia; ie, bowed extremities, such as short-limb craniosynostotic and normocephalic campomelic varieties.[3] This not only was confusing, but also implied a pathogenetic relationship between different bowing conditions. It also served to divert attention from the fact that bowing of the extremities is a nonspecific sign of etiologically different conditions. In our opinion, the term campomelic dysplasia should be reserved strictly for a single distinct entity, as reported originally by Spranger et al[2] and Maroteaux et al.[4] Attempts to bring order to the vast array of conditions with congenitally bent or bowed legs should not create new confusion by using the same or similar names for different disorders. We reviewed the features of classic campomelic dysplasia to establish firm criteria with which to separate it from other disorders that share the sign of congenitally bowed extremities.

From the Department of Pediatrics, University of California, San Francisco (Dr Hall), and the Kinderklinik, University of Mainz, Germany (Dr Spranger).

Reprint requests to M648, Department of Pediatrics, University of California, San Francisco, CA 94143 (Dr Hall).

SUBJECTS AND METHODS

Six new cases from the Skeletal Dysplasia Registry of the Children's Hospital of the University of Mainz, Germany, and 37 case reports from the literature[3-19] form the basis of this report. Since only a few case reports contained information on every aspect of the disorder, the incidence figures were frequently developed on fewer than 43 cases. Some clinical and roentgenographic features, such as long philtrum, small mouth, hallux deviation, brachydactyly, and nonmineralization of thoracic pedicles, were often not commented on by authors or in some of our patients' charts; in these cases, the listing of such features in the tables was based solely on our observations of a patient's photographs and roentgenograms. All six subjects of the present series died between 2 and 34 days of age, and 27 of 31 cases from the literature also died early. For this reason, no specific data will be given on mental retardation, although one long-term survivor is severely retarded.[4]

RESULTS

Gestational data, clinical features, roentgenographic abnormalities, and major pathological findings of the 43 cases are listed in Tables 1 through 3, and will be discussed later. Gestational data that were normal or not pertinent were omitted from the tables. Notably, we found no increased maternal exposure to drugs or gestational difficulties except for a 36% (nine/25) incidence of polyhydramnios. A genetic analysis of the families of our six patients showed that case 5 had a similarly affected sibling. This sibling's sex is unknown and the child is not tabulated in our series because we could not verify the medical information. The mean maternal (23.6 years) and paternal (26.8 years) ages at the time of the birth of their affected children were normal, as were those of the parents reported in the literature.

A total of 17 patients, including our cases 1 and 5, had karyotypes determined. Eight of 17 (47%) had 46,XY karyotypes, despite being phenotypic females. The breakdown of these results is in Table 4. The results of numerous laboratory studies are not listed. They included the determination of levels of serum calcium, phosphorus, alkaline phosphatase, urine amino acids, and glycosaminoglycans, all of which were normal.

Table 1.—Gestational Data and Clinical Features* in Campomelic Dysplasia

Data/Features	Present Series, 6 Cases							Literature, 37 Cases		Combined Total, 43 Cases		
	1	2	3	4	5	6	Total, Average	Total	Average	Total	Average	% (Percentile)
Duration of gestation, wk	40	40	38	...	40	40	39.6	+(31)†	38.7	**+(36)‡**	38.8	...
Phenotypic sex of patient	M	F	F	F	F	F	**F5, M1**	F24, M7	...	**F29, M8**	...	F78, M22
Birth weight, kg	2.3	2.6	3.8	...	3.4	3.6	3.1	+(28)	2.7	**+(33)**	2.7	(10)
Birth length, cm	39	46	...	...	47	52	46	+(20)	40.1	**+(24)**	41.1	(3)
Birth head circumference, cm	...	40	38.5	...	...	...	39.2	+(12)	35.6	**+(14)**	36.1	(90)
Craniofacies												
Macrocephaly	...	+	+	...	—	—	**2/4**	11/20	...	**13/24**	...	54
Large fontanels/sutures	—	+	+	...	+	—	**3/5**	8/15	...	**11/20**	...	55
"Slit-like" eyes	...	...	+	+	—	...	**2/3**	8/14	...	**10/17**	...	59
Hypertelorism	...	+	—	...	...	+	**2/3**	8/14	...	**10/17**	...	59
Flat nasal bridge	+	—	+	...	...	+	**3/4**	20/20	...	**23/24**	...	96
Long philtrum	...	...	+	...	...	+	**2/2**	13/14	...	**15/16**	...	94
Small mouth	...	...	+	...	...	+	**2/2**	12/12	...	**14/14**	...	100
Cleft palate	—	+	—	...	+	+	**3/5**	21/25	...	**24/30**	...	80
Micrognathia	+	+	+	+	+	+	**6/6**	28/28	...	**34/34**	...	100
Abnormal ears§	+	+	+	...	+	...	**4/4**	20/20	...	**24/24**	...	100
Limbs												
Pretibial skin dimples	+	—	+	...	—	+	**3/5**	24/25	...	**27/30**	...	90
Talipes equinovarus	+	+	+	...	+	+	**5/5**	27/27	...	**32/32**	...	100
Halux (medial) deviation	...	...	...	...	+	+	**2/2**	5/6	...	**7/8**	...	87.5
Hypotonia	+	+	...	...	+	+	**4/4**	9/9	...	**13/13**	...	100

*The frequency of other clinical features such as bowing, brachydactyly, heart defects are in Tables 2 and 3.
†Number of patients in literature providing data.
‡Total of patients in literature and present series with sign.
§Means ears are either abnormal in size, shape, or position.

COMMENT

The clinical picture that has emerged from this study (Table 1) is that of a low-normal weight, term newborn with a disproportionately large, dolichocephalic head (Figure, F) and disproportionate shortness, particularly of the lower extremities. The facies (Figure, E) is clearly abnormal with micrognathia, small mouth, cleft palate, long philtrum, flat nasal bridge, hypertelorism, "slit-eyes" (narrow palpebral fissures), and abnormal ears. The bell-shaped chest (Figure, A) is small, giving the abdomen the appearance of being large and protuberant. The upper extremities may be slightly short but are rarely bowed. The hands show mild brachydactyly and various degrees of clinodactyly (Figure, C and D). The lower extremities show symmetrical anterior bowing with pretibial dimples and talipes equinovarus (Figure, A, B, K, and L). Hypotonia, medial deviation of the hallux (Figure, M), and dislocations at the hip, elbows, or fingers are frequently present. Difficult respirations, apneic episodes, cyanosis, and feeding difficulties persist until death, which occurs within the first month of life in the majority of cases. Major abnormalities appearing on roentgenograms (Table 2) in addition to the characteristic lower-extremity bowing include the following: (1) absent or hypoplastic scapulae (Figure, A and J), (2) nonmineralization of the thoracic pedicles (Figure, H), and (3) narrow, vertical ilial bones (Figure, A and L). Other particularly useful diagnostic features are the hypoplastic cervical vertebrae (Figure, G), widely spaced ischial bones (Figure, A and L), and absence of the distal femoral and proximal tibial epiphyses (Figure, A). It should be emphasized that the femoral bones are not broad and their shortening is due primarily to the bowing, whereas the tibial bones are often broad and short (Figure, K) in addition to being bowed.

Some anatomic features (Table 3) are of diagnostic importance, particularly in patients who die without adequate clinical or roentgenographic documentation. Findings such as absent or hypoplastic olfactory bulbs (tracts) and hypoplastic trachea or cartilaginous rings with or without heart defects and hydronephrosis would be highly suggestive of campomelic dysplasia in a child with congenital symmetrically bowed lower extremities. The surprisingly high frequency of hydronephrosis (38%) and congenital heart defects (21%) has not been previously emphasized in campomelic dysplasia.

The differential diagnosis of campomelic dysplasia must initially include all bone dysplasias with congenital bowing[5,6] and early death.[21-23] Among the well-established disorders, the differentiation is not difficult using the findings in Tables 1 through 3. However, we have had some difficulty with diastrophic dwarfism[24] and Larsen's syndrome[25] in the neonatal period. These two disorders share with campomelic dysplasia the clinical features of cervical vertebral anomalies, cleft palate, joint dislocations, talipes equinovarus, clinodactyly, bowed extremities, and laryngotracheal abnormalities.[26,27] The campomelic syndrome also shares abnormal ears, micrognathia, medial deviation of the hallux, and brachydactyly with dias-

Table 2.—Frequency of Roentgenographic Abnormalities in Campomelic Dysplasia

Abnormalities	Present Series, 6 Cases 1	2	3	4	5	6	Total	Literature, 37 Cases, Total	Combined, 43 Cases, Total (%)
Limbs									
Moderate/severe bowed femora and tibiae*	+	+	+	+	+	+	**6/6**	36/36	**42/42** (100)
Absent distal femoral epiphyses	+	+	+	+	+	+	**6/6**	23/28	**29/34** (85)
Absent proximal tibial epiphyses	+	+	+	+	+	+	**6/6**	25/26	**31/32** (97)
Absent talus	+	—	—	—	+	—	**2/6**	19/22	**21/28** (75)
Normal/mild bowed humeri and radii	+	+	+	+	+	+	**6/6**	35/35	**41/41** (100)
Brachydactyly	...	...	+	+	+	+	**4/4**	9/15	**13/19** (68)
Widened tips to distal phalanges	...	+	+	...	+	+	**4/4**	4/9	**8/13** (62)
Clinodactyly	...	+	+	...	+	+	**4/4**	6/10	**10/14** (71)
Thorax and spine									
Absent mineralization of sternum	+	...	...	...	+	+	**3/3**	10/11	**13/14** (93)
Small bell-shaped chest	+	+	+	+	+	+	**6/6**	14/17	**20/23** (87)
Thin ribs	—	+	—	...	—	—	**1/5**	15/17	**16/22** (73)
11 Ribs	—	+	+	+	+	—	**4/6**	14/15	**18/21** (86)
Severely hypoplastic scapulae	+	+	+	+	+	+	**6/6**	30/30	**36/36** (100)
Nonmineralized thoracic pedicles	+	+	+	+	+	+	**6/6**	16/16	**22/22** (100)
Abnormal cervical vertebra†	+	+	+	...	+	+	**5/5**	23/25	**29/30** (97)
Flattened lumbar/lower thoracic vertebra	+	...	+	...	+	—	**3/4**	7/12	**10/16** (62)
Pelvic area									
Narrow vertical ilial bones	+	+	+	+	+	+	**6/6**	27/27	**33/33** (100)
Widely spaced ischial bones	+	+	+	+	+	+	**6/6**	27/27	**33/33** (100)
Hip dislocations (or other areas)	+	+	—	—	—	—	**2/6**	17/23	**19/29** (65)

*Fibula may be bowed with or without shortening.
†Cervical vertebra hypoplastic, poorly mineralized or in kyphotic position.

Table 3.—Major Pathological Findings in Campomelic Dysplasia*

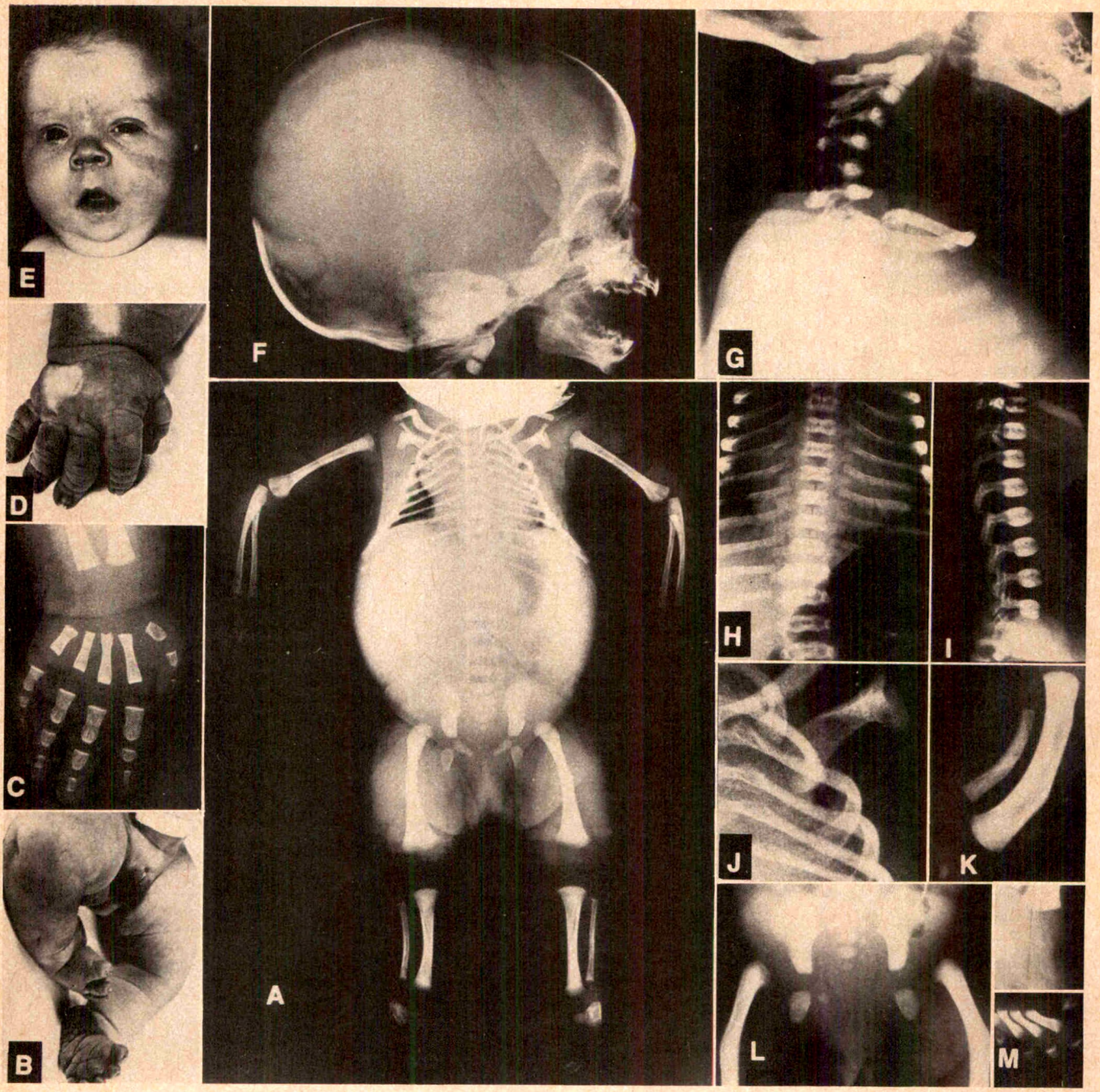
Findings	Present Series, 6 Cases 1	2	3	4	5	6	Total	Literature, 27 Cases, Total	Combined, 33 Cases, Total (%)
CNS									
Hydrocephalus	—	+	+	...	...	—	**2/4**	4/17	**6/21** (28)
Absence/hypoplasia of olfactory tract or bulbs	—	—	—	...	...	—	**0/4**	4/18	**4/22** (18)
Intercranial intracranial hemorrhage	—	+	—	...	...	—	**1/4**	4/19	**5/23** (22)
Cardiorespiratory systems									
Heart anomalies/defects	—	—	—	...	—	+	**1/5**	7/25	**8/30** (27)
Hypoplastic trachea and/or cartilaginous rings	+	—	+	...	...	—	**2/4**	10/16	**12/20** (60)
Pulmonary aspiration, atelectasis or congestion	—	+	—	...	...	+	**2/4**	12/17	**14/21** (67)
Pulmonary hemorrhage	+	—	—	...	...	+	**2/4**	3/17	**5/21** (24)
Renal									
Hydronephrosis	+	—	+	...	...	+	**3/4**	5/17	**8/21** (38)

*See comments regarding gonads in text.

Table 4.—Comparison of Phenotypic Sex and Karyotypic Sex in 17 Patients With Campomelic Dysplasia

Authors	Cases	Phenotypic Sex	Karyotypic Sex
Kozlowski et al[5]	1	F	F
Storer and Grossman[7]	1	F	F
	2	F	F
Schmickel et al[11]	1	F	F
Lee et al[6]	3	F	F
	2	F	F
	1	M	M
Maroteaux et al[4]	1	M	M
Present report	1	M	M
	5	F	M
Hoefnagel et al[16]	1	F	M
	2	F	M
Engel et al[20]*	1	F	M
Rolland et al[19]	1	F	M
Gardner et al[18]	1	F	M
Hovmöller et al[17]	1	F	M
	2	F	M

*Excluded from clinical tables because no comment was made in the report on limb bowing.



(A) Full-body posteroanterior view. (B) Tibial bowing with pretibial dimples and equinovarus deformity. (C, D) Brachydactyly, clinodactyly, and widened distal phalangeal tips. (E) Facies showing flat nasal bridge, long philtrum, small mouth, and micrognathia. (F) Macrocephaly with large anterior fontanel. (G) Hypoplastic cervical vertebrae. (H) Nonmineralized thoracic pedicles. (I) Normal lower thoracic and lumbar spine. (J) Hypoplastic scapula. (K) Short, broad, and anteriorly bowed tibia. (L) Vertically narrow ilial bones with widely spaced ischial bones and bowed femora. (M) Equinovarus deformity with hallux deviation.

trophic dwarfism, and flat nasal bridge and hypertelorism with Larsen's syndrome.[25] Comparison of the scapulae, thoracic pedicles, and ilial bones between these entities should allow a secure diagnostic separation. Of course, the multitude of unknown types of bone disorders with congenital bowing will remain a problem; however, using the features tabulated here, it should be possible to tell whether or not a patient has campomelic dysplasia.

The association of a skeletal dysplasia in a karyotypic 46,XY male who has female external genitalia and vagina, uterus, and Fallopian tubes is difficult to explain. Prior to seeing case 5, we were reluctant to accept this association. Our case 5 had classic features of campomelic dysplasia, female genitalia, and a male karyotype. Unfortunately, no autopsy was performed, so the appearance of the gonads is unknown. Most of the reports[16,18-20] of gonadal studies did not adequately document the clinical and roentgenographic aspects, leaving some doubt regarding the diagnosis of campomelic dysplasia; however, Hovmöller and associates[17] reported two such instances that were well documented. The pathological findings were adequately investigated in three of the previously mentioned reports, and all found either poorly differentiated ovarian tissue in the ovarian fossa[16,17] or gonadal tissue with an embryonal testicular pattern.[20] All of these patients also had normal-appearing external female genitalia, vagina, uterus, and Fallopian tubes. This sex-reversal phenomenon may explain the "female" preponderance of 29:8 among our tabulated cases. A comparison (Table 4) of the phenotypic sex and karyotypic sex in all patients who were karyotyped,[4-7,11,16-20] including our cases 1 and 5, show a more equal sex ratio of 20:14, female to male.

The inheritance pattern of campomelic dysplasia is not yet definitely established. Present evidence suggests an autosomal recessive mode of inheritance based on similarly affected mixed-sex siblings of normal parents as reported by Thurmon et al,[8] Shafai and Schwartz,[9] and ourselves (case 5), plus a report of consanguinity by Cremin and associates.[28] Our review of the published data show a total of 60 pregnancies, 15 abortions, 25 probands, 17 normal siblings (seven male, six female, four sex unknown) and three similarly affected siblings. Case 1 from Thurmon et al (Table 4, no. 9)[8] is not included as a similarly affected sibling because the patient's condition was very poorly documented and he was also a half-sibling. Once the probands and abortions are excluded, a 15% incidence (three/20) of similarly affected siblings is obtained that is closest to an expected autosomal recessive gene occurrence of 25%.

Campomelic dysplasia is a distinct syndrome, with all of its major clinical and roentgenographic features occurring with a greater than 50% frequency. Three of its regular roentgenographic features, namely hypoplastic scapulae, nonmineralized thoracic pedicles, and vertically narrow ilial bones, are rare findings in themselves and unique in combination. With adequate documentation, campomelic dysplasia should not be confused with other disorders involving congenital bowing of the lower extremities.

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References

1. International nomenclature of constitutional diseases. *J Pediatr* 93:614-616, 1978.
2. Spranger J, Langer LO, Maroteaux P: Increasing frequency of a syndrome of multiple osseous defects. *Lancet* 2:716, 1970.
3. Khajavi A, Lachman R, Rimoin D, et al: Heterogeneity in the campomelic syndromes: Long and short bone varieties. *Radiology* 120:641-647, 1976.
4. Maroteaux P, Spranger J, Opitz JM, et al: Le syndrome campomélique. *Presse Med* 79:1157-1162, 1971.
5. Kozlowski K, Bützler HO, Galatius-Jensen F, et al: Syndromes of congenital bowing of the long bones. *Pediatr Radiol* 7:40-48, 1978.
6. Lee FA, Isaacs H, Strauss J: The "campomelic" syndrome. *Am J Dis Child* 124:485-496, 1972.
7. Storer J, Grossman H: The campomelic syndrome. *Radiology* 111:673-681, 1974.
8. Thurmon TF, Defraites EB, Anderson EE: Familial campomelic dwarfism. *J Pediatr* 83:841-843, 1973.
9. Shafai T, Schwartz L: Campomelic syndrome in siblings. *J Pediatr* 89:512-513, 1976.
10. Bain AD, Barrett HS: Congenital bowing of the long bones: Report of a case. *Arch Dis Child* 34:516-524, 1959.
11. Schmickel RD, Heidelberger KP, Poznanski AK: The campomelique syndrome: *J Pediatr* 82:299-302, 1973.
12. Weiner DS, Benfield G, Robinson H: Campomelic dwarfism: Report of a case and review of the salient features. *Clin Orthop* 116:29-31, 1976.
13. Ameri MR, Alebouyeh M, Amirfeyz M, et al: Das kampomele Syndrom. *Mschr Kinderheilk* 126:687-689, 1978.
14. Bianchine JW, Risemberg HM, Kanderian SS, et al: Campomelic dwarfism. *Lancet* 1:1017-1018, 1971.
15. Becker MH, Finegold M, Genieser NB, et al: Campomelic dwarfism. *Birth Defects* 2:113-118, 1975.
16. Hoefnagel D, Wurster-Hill DH, Dupree WB, et al: Campomelic dwarfism associated with XY-gonadal dysgenesis and chromosome anomalies. *Clin Genet* 13:489-499, 1978.
17. Hovmöller ML, Osuna A, Eklöf O, et al: Campomelic dwarfism: A genetically determined mesenchymal disorder combined with sex reversal. *Hereditas* 86:51-62, 1977.
18. Gardner LI, Assemany SR, Neu RL: XY female: Antiandrogenic effect of oral contraceptive? *Lancet* 2:667-668, 1970.
19. Rolland M, Dupic Y, Bergès J-D, et al: Le syndrome camptomélique: A propos d'une observation, abstracted. *Pediatrie* 30:860-861, 1975.
20. Engel W, Reinwein H, Bombel D, et al: Multiple missbildungen bei einem Mädchen mit dem Karyotypus 46 XY, 17g+. *Humangenetik* 6:311-325, 1968.
21. Houston CS, Awen CF, Kent HP: Fatal neonatal dwarfism. *J Canad Assoc Radiol* 23:45-61, 1972.
22. Curran JP, Sigmon BA, Opitz JM: Lethal forms of chondrodysplastic dwarfism. *Pediatrics* 53:76-85, 1974.
23. Spranger J, Grimm B, Weller M, et al: Short-rib polydactyly (SRP) syndromes, types Majewski and Saldino-Noonan. *Z Kinderheilkd* 116:73-94, 1974.
24. Langer LO: Diastrophic dwarfism in early infancy. *Am J Roentgenol* 89:399-404, 1965.
25. Silverman FN: Larsen's syndrome: Congenital dislocation of the knees and other joints, distinctive facies, and frequently, cleft palate. *Ann Radiol* 15:297-328, 1971.
26. Walker BA, Scott CI, Hall JG, et al: Diastrophic dwarfism. *Medicine* 51:41-59, 1972.
27. Rønningen H, Bjerkreim I: Larsen's syndrome. *Acta Orthop Scand* 49:138-142, 1978.
28. Cremin BJ, Orsmond G, Beighton P: Autosomal recessive inheritance in campomelic dwarfism. *Lancet* 1:488-489, 1973.

Acute Isoniazid Poisoning in Childhood

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• Acute isoniazid poisoning is uncommon in children. Only 27 cases, to our knowledge, have been reported in the literature. Often, the first observation is of uncontrollable convulsions. The metabolic alterations are often striking and the treamtent has mainly been supportive, with the judicious use of pyridoxine hydrochloride in those cases in which a history of ingestion of isoniazid is obtained. The response to the administration of pyridoxine has been difficult to evaluate.

(*Am J Dis Child* 134:290-292, 1980)

Although ineffective therapy of prolonged, generalized seizures (status epilepticus) is commonly associated with inadequate doses of anticonvulsants, failure to recognize other causes of persistent, generalized convulsions may lead to otherwise unnecessary morbidity and mortality. Since the introduction of isoniazid in 1952, periodic reports of intentional or accidental intoxications complicated by generalized convulsions have appeared.[1-8] Such poisoning may present a dangerous, life-threatening situation in which medical management must be pursued aggressively. Awareness of such poisonings is particularly relevant to children, in whom isoniazid is a commonly used antituberculous agent. Four cases of isoniazid poisoning have been encountered at Martin Luther King, Jr, General Hospital, Los Angeles.

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REPORT OF CASES

CASE 1.—A 1½-year-old boy was brought to the Pediatric Acute Care Clinic in the midst of a general convulsion. According to his mother, the child had been in good health one hour prior to admission. Shortly after the patient's arrival, a 2½-year-old sibling who was convulsing and a 4-year-old sibling who was lethargic were both brought into the clinic by their father. An empty bottle of 300-mg isoniazid tablets found in the home was brought with the two siblings, one of whom was currently receiving treatment with prophylactics for tuberculosis. Results of physical examination of the 1½-year-old child at the time of admission were unremarkable except for generalized seizure activity. He was afebrile and had no localizing neurological signs. Before the history of ingestion was elicited, the patient was given dextrose (1 g/kg) and a total of 10 mg of diazepam (Valium) intravenously without any noticeable decrease in seizure activity. The additional administration of phenytoin (Dilantin), 150 mg intravenously, also was without avail. Continued seizure activity was accompanied by respiratory embarrassment that necessitated endotracheal intubation and intermittent ventilation. The convulsions ceased after the administration of 6 mL of paraldehyde rectally. The entire duration of seizure activity was 2½ hours. After obtaining a history of presumptive isoniazid ingestion, the patient was also given 150 mg of pyridoxine hydrochloride intravenously. Abnormal laboratory findings at the time of admission included the following values: WBCs, 21,000/cu mm, with a lymphocytosis; ketonuria; serum bicarbonate, 13 mEq/L; and, glucose, 355 mg/dL. An initial arterial blood sample showed a severe metabolic acidosis, with a pH of 7.13, a base excess of −15 mEq/L and a P_{CO_2} of 48 vol%. A chest roentgenogram showed a right upper lobe infiltrate. Serum isoniazid level was 103 μg/mL, almost ten times the maximum therapeutic level. Analyses of isoniazid levels were performed by the University of Southern California-Los Angeles County Toxicology Laboratory, using a modification of Maher's method.[9]

The morning after admission, no further seizure activity was noted. The remaining hospital course was complicated by postextubation laryngeal edema that required a tracheostomy. The patient's condition improved thereafter and he was discharged after a 20-day hospitalization period. When seen in the follow-up clinic one week after discharge, the patient was in good health without evidence of neurologic deficit.

CASE 2.—The 2½-year-old sibling of case 1 was also noted to have generalized seizure activity on admission. Control was achieved by the administration of 10 mg of diazepam and 100 mg of pyridoxine hydrochloride intravenously. The history indicated that this sibling was receiving isoniazid for treatment of tuberculosis.

Physical examination at the time of admission showed an actively convulsing boy without lateralizing neurological signs. Vital signs were within normal limits. Pertinent laboratory values were as follows: WBCs, 21,000/cu mm; serum bicarbonate, 12 mEq/L; and, serum glucose, 255 mg/dL. The serum isoniazid level was 35 μg/mL.

The patient remained comatose throughout the night, unresponsive to painful stim-

uli, and with sluggishly reactive pupils. By the next morning, the patient was fully alert, with no further seizure activity. He was discharged home after four days and is being followed up at the Public Health Clinic for tuberculosis.

CASE 3.—That same night, the 4-year-old sibling of case 1 was noted to be lethargic, and isoniazid poisoning was suspected, although no seizure activity was observed. His medical history indicated that he was also taking isoniazid for a positive PPD and roentgenographic evidence of perihilar adenopathy. Physical examination showed a 20-kg boy who was mildly lethargic without lateralizing neurological signs. Complete blood cell counts and blood chemistry levels were normal. Chest roentgenogram showed perihilar adenopathy. On the morning after admission, the patient was alert and active. A blood sample was sent for an isoniazid assay. The laboratory was unable to provide this information. The patient was discharged and on follow-up in the Public Health Clinic was in satisfactory health.

CASE 4.—A 16-year-old girl was brought to the pediatric emergency room in the midst of a general convulsion. A partially empty bottle of isoniazid tablets was found near the patient, and a presumptive diagnosis of isoniazid overdose was made. The administration of 10 mg of diazepam intravenously temporarily interrupted the seizures; however, depressed respiratory function necessitated intubation. Fifteen minutes later, seizure activity recurred and the patient was subsequently given 15 mL of paraldehyde rectally and 300 mg of pyridoxine hydrochloride intravenously, with immediate cessation of all seizure activity. The patient was comatose, with no response to any external stimuli, her pupils were pinpoint, and her deep tendon reflexes were severely decreased. Laboratory findings included a serum pH of 6.84; serum glucose level of 324 mg/dL; and a WBC count of 16,800/cu mm. The severe metabolic acidosis was treated with a total of 180 mEq of sodium bicarbonate to a pH of 7.34.

Approximately one hour later, the patient's blood pressure suddenly fell to nonpalpable levels. A dopamine hydrochloride infusion was begun and her blood pressure rose to 50/20 mm Hg. Six hours after admission, the patient had a cardiac arrest and was resuscitated successfully. Shortly thereafter, a second cardiac arrest ensued, resuscitation efforts were unsuccessful, and the patient died after a seven-hour hospitalization. A serum isoniazid determination obtained on admission was 127 μg/mL. Permission for autopsy was refused.

COMMENT

Since the introduction of isoniazid in 1952, 27 cases in children of intentional or accidental isoniazid intoxication have, to our knowledge, appeared in the English-language literature.[1-8] Three of the 27 children died. Two of these deaths occurred among children in an Alaskan Eskimo village who were being given prophylactic isoniazid. There was no detailed description of their clinical course. The other death, reported by Kelso et al[3] in 1965, was that of a 15-year-old girl in whom, after ingestion of 5 g of isoniazid, intractable seizures, oliguria, hypotension, hyperpyrexia, and deep coma developed. She died approximately 70 hours after ingestion.

Among the surviving patients, ages ranged from 15 months to 16 years. Clinical signs and symptoms included nausea, vomiting, hypotension, leukocytosis, hyperpyrexia, respiratory distress, intractable seizures, and coma.

The amount of isoniazid ingested varied from 0.9 to 20 g and serum isoniazid levels were between 8 and 35 μg/mL in the five cases where levels were obtained (the therapeutic range is considered to be 0.5 to 12 μg/mL). Generalized seizures have been described previously in patients receiving as little as 35 to 40 mg/kg of isoniazid intramuscularly,[10] and 200 mg/kg is thought to be an obligatory convulsant dose in man.

The rate of elimination of isoniazid is a major determining factor in the manifestation of toxicity. The primary route of isoniazid inactivation is by acetylation. Persons may be identified as either slow, intermediate, or fast acetylators. Approximately 60% of all whites and blacks are slow acetylators, as opposed to only 10% of all orientals and Eskimos.[11] Consequently, both a higher incidence and a more severe form of toxicity might be expected in these former individuals.

The metabolic alterations produced by isoniazid intoxication are substantial and have included severe metabolic acidosis, ketonuria, hyperglycemia, mild hyperkalemia, and increased urinary excretion of pyridoxine.[5] These observed changes are due to a complex of pharmacological alterations involving pyridoxine metabolism. First, isoniazid lowers the effective tissue and serum level of pyridoxine through the formation of isoniazid-pyridoxine hydrazones that are rapidly excreted via the kidney.[12] Second, these same hydrazones competitively inhibit pyridoxine kinase, the activating enzyme that converts pyridoxine to the physiologically active pyridoxal phosphate.[12,13] Third, isoniazid inactivates pyridoxal phosphate-containing enzymes through the same coupling mechanism. Specific enzyme functions involved include amino acid transaminases and decarboxylases. In addition, a reduction in the pyridoxine level has an adverse effect on both the formation and catabolism of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA).[12,13] The reduction in GABA turnover may explain, at least in part, the intractable seizures produced by isoniazid intoxication.

There is laboratory and clinical evidence that the antagonistic action of isoniazid on pyridoxine does not completely explain the metabolic alterations observed. This implies, perhaps, a wider spectrum of metabolic disturbance than that of the pyridoxal-dependent pathways alone.

In laboratory studies, administration of pyridoxine failed to protect animals from isoniazid-induced convulsions, whereas 50% of all animals given 200 mg/kg of isoniazid were protected by the administration of niacinamide (400 mg/kg).[12] Furthermore, there are clinical accounts of patients who have taken large doses of isoniazid and pyridoxine in combination, but who nevertheless manifested severe convulsions.[4] At the molecular level, isoniazid interferes with nicotinamide adenine dinucleotide (NAD)-catalyzed reactions.[4,14] Nicotinamide adenine dinucleotide is recognized as an essential component of the energy-producing reactions of glycolysis and the tricarboxylic acid cycle. The introduction of isoniazid into the NAD molecule forms an inactive analogue of NAD that seriously disrupts intermediary metabolism.[14] Recently, niacinamide was noted to be as effective as pyridoxine in reversing isoniazid-induced hyperkinesis.[15] In light of these observations, there may

be justification on both clinical and biochemical grounds for the use of niacinamide in the treatment of isoniazid poisoning.

In the reported pediatric cases, pyridoxine was the most commonly used therapeutic agent. There were no case reports of therapy with niacinamide. The dosage of pyridoxine hydrochloride varied widely from a low of 20 mg to a high of 1,500 mg per 1,000 mg of isoniazid ingested. The dosage schedule varied from a single injection to four doses given over a period of 48 hours.

The concurrent use of anticonvulsants such as diazepam, phenobarbital, paraldehyde, phenytoin makes the evaluation of therapy with pyridoxine difficult. Phenytoin may even be toxic to those patients with a high serum isoniazid level.[16] Isoniazid is a potent inhibitor of phenytoin metabolism in man. Its mode of action seems to be as a noncompetitive inhibitor of the parahydroxylation of phenytoin, a major step in elimination of phenytoin from the body. The principal manifestations of phenytoin toxicity are lethargy, nystagmus, and ataxia. These factors are difficult to recognize in the comatose patient and may further complicate the clinical picture of isoniazid poisoning. Furthermore, clinical studies have shown that those patients phenotypically identified as slow inactivators of isoniazid are at an increased risk for phenytoin intoxication.[16]

The key issues for the clinician are the timely recognition of the offending agent and the successful management of the seizures, the metabolic abnormalities, and any resultant complications. Therapy with phenytoin should be avoided when a history of therapy or poisoning with isoniazid is known. The suggested interaction of isoniazid with NAD-catalyzed reactions warrants further clinical observations regarding the use of niacinamide along with pyridoxine in the treatment of isoniazid poisoning.

Nonproprietary Names and Trademarks of Drugs

Dopamine hydrochloride—*Intropin.*
Isoniazid—*Niconyl, Nydrazid.*

References

1. Katz BE, Carver MW: Acute poisoning with isoniazid treated by exchange transfusion. *Pediatrics* 18:72-75, 1956.
2. Livingston S, Peterson D, Peck J: Convulsive reaction in a two-year-old child following the accidental ingestion of an overdosage of isoniazid. *Pediatrics* 18:77-79, 1956.
3. Kelso T, Toll W Jr, Pinkerton DC, et al: Death due to intentional overdosage of isoniazid: A case report. *J Forensic Sci* 10:313-318, 1965.
4. Terman DS, Teitelbaum DT: Isoniazid self-poisoning. *Neurology* 20:299-304, 1970.
5. Brown CV: Acute isoniazid poisoning. *Am Rev Respir Dis* 105:206-216, 1972.
6. Mottram PE, Johnson PB, Hoffman JE: Isoniazid toxicity: Reversal with pyridoxine. *Minn Med* 57:81-83, 1974.
7. McKenzie SA, MacNab AJ, Katz G: Neonatal pyridoxine responsive convulsions due to isoniazid therapy. *Arch Dis Child* 51:567-568, 1976.
8. Coyer JR, Nicholson DP: Isoniazid-induced convulsions. *South Med J* 69:294-297, 1976.
9. Maher JR: Quantitation of INH in body fluids. *Am Rev Tuberculosis Respir Dis* 76:852-861, 1957.
10. Reilly RH, Killam MS, Marshall EH, et al: Convulsant effects of isoniazid. *JAMA* 152:1317-1321, 1953.
11. Ellard GA: Variations between individuals and populations in the acetylation of isoniazid and its significance for the treatment of pulmonary tuberculosis. *Clin Pharmacol Ther* 19:610-625, 1976.
12. Holtz P, Palm D: Pharmacological aspects of vitamin B_6. *Pharmacol Rev* 16:113-178, 1964.
13. McCormick DB, Guirard BM, Snell EE: Comparative inhibition of pyridoxal kinase and glutamic acid decarboxylase by carbonyl reagents. *Proc Soc Exp Biol Med* 104:554-557, 1960.
14. DiAugustine RP: Formation in vitro and in vivo of the isonicotinic acid hydrazide analog of nicotinamide adenine dinucleotide by lung nicotinamide adenine dinucleotide glycohydrolase. *Mol Pharmacol* 12:291-298, 1976.
15. Brenner A, Wapnir RA: A pyridoxine-dependent behavioral disorder unmasked by isoniazid. *Am J Dis Child* 132:773-776, 1978.
16. Kutt H, Brennan R, Dehejia H, et al: Diphenyhydantoin intoxication. *Am Rev Respir Dis* 101:377-383, 1970.

Lip Pits, Cleft Lip and/or Palate, and Congenital Heart Disease

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• **Three individuals in whom lip pits and cleft lip and/or cleft palate were found in association with congenital heart disease are described. These individuals did not have the characteristics of previously delineated syndromes in which lip pits occur, including Vanderwoude syndrome, popliteal pterygium syndrome, and orodigitofacial dysostosis. Literature review failed to show any previously reported cases in which pits were observed in association with congenital heart disease.**

(*Am J Dis Child* 134:293-295, 1980)

Bilateral, congenital, lower-lip pits is a rare anomaly most often seen in association with autosomal dominant inheritance of cleft lip and/or cleft palate (Vanderwoude syndrome).[1] Lip pits may also be seen as part of the popliteal pterygium syndrome,[2,3] and orodigitofacial dysostosis.[4] The following three cases are, to our knowledge, the first reported in which the distinctive and rare combination of lip pits and cleft lip and/or cleft palate has occurred with congenital heart disease.

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REPORT OF CASES

CASE 1.—This male infant was born on June 4, 1978, to a gravida 3, para 2, abortus 1 woman after a pregnancy complicated only by morning sickness in the tenth through 18th weeks. The father was 24 years old, the mother 25 years at the time of the birth. Drug exposure during gestation included vitamins and iron throughout pregnancy and incidental exposure to acetaminophen, aspirin, and calcium carbonate antacid, all in the second and third trimesters. Maternal weight gain was 9 kg; fetal activity was noted around the 16th week and was noted subjectively as less than in the mother's first pregnancy.

Following an easy vaginal delivery, complicated by late meconium staining, a 4,140-g, 51-cm dysmorphic male infant was born. He was transferred to Children's Orthopedic Hospital and Medical Center, Seattle, because of apparent congenital heart disease.

Abnormalities noted by physical examination included: complete bilateral clefts of the lip and palate; bilateral lip mounds (Fig 1); concave, slightly hypoplastic fingernails and toenails; broad halluces; a prominent crease between the first and second toes; and an inferior accessory nipple on the left. Neurologically, he was vigorous and normal. The lip excrescences were approximately 5 mm high and placed symmetrically on either side of the midline in the vermilion portion of the lower lip. Tiny blind dimples were present on the tip of each of these structures.

On auscultation, a holosystolic murmur and a single second heart sound were heard. There was dextroposition of the cardiac silhouette on the chest roentgenogram. Arterial blood sampling supported the clinical impression of cyanosis with severe right-to-left shunting. Corrected transposition of the great vessels, dextroposition, ventricular septal defect, patent ductus arteriosum, patent foramen ovale, and pulmonary atresia were observed at cardiac catheterization. Medical means were used to maintain the patent ductus until a Blalock-Taussig shunt could be formed on the third day of life.

The family history was negative for congenital heart disease. A distant paternal relative did have cleft palate, but this was a U-shaped cleft associated with micrognathia and probably represents the Pierre Robin malformation complex. The parents had no lip pits, lip mound, or submucous or uvular clefting on physical examination. Chromosomal studies of peripheral blood, including R banding, were normal (46,XY).

CASE 2.—This male infant was born on April 19, 1977, to a 21-year-old gravida 2, para 2 mother and a 24-year-old father. The pregnancy was uncomplicated, with quickening reported at three to four months and with the total weight gain being 7.7 kg. Known chemical exposures were limited to vitamins and iron and one to two packs of cigarettes per day throughout pregnancy.

The 2,970-g, 48-cm male infant was evaluated as a newborn at Children's Orthopedic Hospital and Medical Center because of

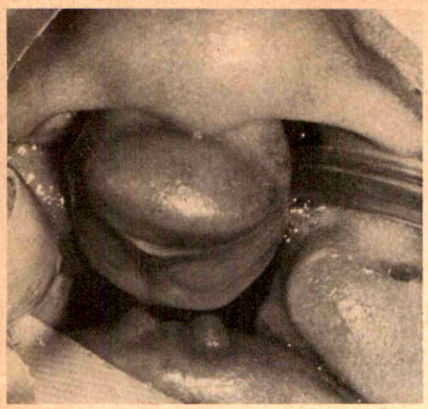

Fig 1.—Nose and mouth (case 1). Bilateral clefts and lower-lip excrescences are demonstrated. Tiny, blind dimples cannot be seen.

Fig 2.—Lip pits with surrounding mounds (case 2), as well as other facial features described in text.

multiple malformations and congenital heart disease.

Posterior cleft palate, bilateral symmetrically placed lip pits and mounds (Fig 2), prominent nasal bridge, small mandible, inferior branchial cleft remnants on the neck, prominent eyes, simple helices, hypoplastic nails, proximally placed thumbs, hypoplastic nipples, redundant posterior neck skin, dislocatable hips, and cryptorchidism with bilateral inguinal hernias were demonstrable by physical examination. Neurologically, he was hypotonic and hyporeflexic and he showed decreased reactivity; mild optic atrophy was present.

The patient had a systolic ejection murmur and paroxysmal ventricular tachycardia. Congestive heart failure developed in the week after birth and cardiac catheterization was performed. Abnormalities (by catheterization and postmortem examination) included coarctation and tubular hypoplasia of the aortic arch, ventricular septal defects, patent ductus arteriosum, patent foramen ovale, bicuspid aortic valve, subaortic stenosis, and abnormal mitral valve.

Family history was negative for congenital heart disease, clefting, or pits. Parents were free of lip pits or mounds. Chromosomal studies of bone marrow, peripheral lymphocytes, and fibroblasts (including R banding) showed a normal 46,XY constitution.

No operative intervention was undertaken, and despite medical management of congestive heart failure, the child fed poorly, failed to thrive, and died at 4 months of age of recurrent apnea. The described abnormalities and incomplete lobulation of the left lung were observed on postmortem examination.

CASE 3.—This male infant was born on March 31, 1973, to a 28-year-old gravida 5, para 5 mother and 32-year-old father. The pregnancy was free of illness or drug exposure; an older sibling had a viral exanthem at the third month of this gestation, but the illness was said not to have been rubella.

Vaginal delivery was at term. The 3,570-g, 53-cm male infant was noted to have an abnormal lower lip and, when feeding difficulties occurred, a cleft of the hard and soft palate was observed.

His case has been followed at Children's Orthopedic Hospital and Medical Center since he was 12 months of age. Problems have included lip pits, cleft palate, and congenital heart disease. The bilateral pits were removed at 12 months of age. They were nipple-like, asymmetric projections without an obvious tract, but ductile channels with collections of mucous glands were demonstrated histologically. The palate had a right-sided, V-shaped cleft of the soft and posterior half of the hard palate. It too was repaired at 1 year of age.

During his initial hospitalization, a systolic heart murmur was noted. Subsequent evaluation demonstrated a ventricular septal defect, coarctation of the aorta, and pulmonary hypertension.

In addition, the patient has growth failure, enamel hypoplasia, frontal prominence, absent upper lateral incisors, conductive hearing loss and severe articulation problems, and a deep crease between the first and second toes bilaterally. He is neurologically and developmentally normal except for the speech and language disability.

The family history was negative for lip pits or congenital heart disease. A paternal second cousin is said to have cleft lip and palate without associated anomalies. The condition of an older sister of the patient has been diagnosed as being Prader-Willi syndrome. Another sibling died perinatally secondary to a nuchal cord. The parents have no pits, mounds, or evidence of clefting. Chromosomal studies of peripheral blood, including R banding, were normal (46,XY).

COMMENT

Congenital lip pits are exceedingly rare.[1-5] These lip pits are characteristically symmetric, blind tracts in the midst of the vermilion part of the lower lip at the point where the pars glabra and pars villosa meet.[5,6] The tracts are about 2 mm in diameter and vary greatly in depth.[6] Occasionally, as in our cases 1 and 3, a tract is not easily demonstrable but, rather, nipple-like mounds are found in the same location as the more typical pits.[7] The presence of blind dimples in case 1 and histologically demonstrable tracts in case 3 supports the contention that the observed structures are homologous to more typical lip pits. Lower-lip pits must be differentiated from commissural pits at the corners of the mouth, which are common and apparently without importance.[8,9]

Lower-lip pits have been seen in only three clearly defined syndromes. Vanderwoude syndrome is characterized by lip pits; cleft lip and/or cleft palate, and hypodontia[10]; autosomal dominant inheritance; incomplete penetrance (80%); and variable expressivity.[1,5,11,12] Principal findings in the popliteal pterygium syndrome[2,3] include pterygia or tissue webs in the popliteal, crural, and oral regions; digital hypoplasia; syndactyly; genitourinary anomalies; and lip pits with cleft lip or palate. Lip pits have also been reported in two individuals with orodigitofacial dysostosis.[4] Besides these syndromes, lip pits have been found in association with clubfoot,[13] isolated syndactyly,[5,14-16] ectodermal dysplasia,[17] ankyloglossia,[18] syngnathia,[19] polythelia,[13,16] and mental retardation.[20] To our knowledge, no previous association of lip pits and congenital heart disease has been published.

Patients ascertained by the presence of facial *clefts* have a notably increased incidence of congenital heart disease.[21] In the study of Shah et al,[21] 31 of 192 consecutive patients with facial clefts had congenital heart disease. Curiously *absent* from the cases of facial clefts and congenital heart defects were transposition of the great vessels and single ventricle.[21] Ascertainment by the presence of congenital heart disease shows a

10% to 40% incidence of extracardiac anomalies.[22,23] However, extracardiac anomalies are evidently exceedingly rare in patients with transposition of the great vessels. There were no "cephalic end abnormalities" in 196 patients with transposition, in contrast to an overall incidence in all congenital heart disease patients of 6%.[23] Thus, case 1 seems to be the first recorded case of transposition of the great vessels in association with cleft lip and cleft palate.

Shah et al[21] hypothesized that the negative association between transposition and clefting is because the embryologic defect causing the heart lesion precedes palatal development by about two weeks. But Warbrick et al[24] showed that lip pits may be remnants of normally transient lateral sulci whose time of appearance (at around four weeks) and regression (complete by around six to seven weeks) are temporally coincident with conotruncal development of the heart,[21] thereby suggesting a possible embryogenic temporal relationship for the defects found in case 1. We cannot fully explain embryologically the association of malformations seen in case 1, nor will we attempt to interpret the abnormalities in cases 2 and 3.

Each of these cases represent separate, provisionally unique malformation syndromes. Although these three cases may represent different entities, they are reported together because they are apparently the first three instances of association between lip pits with cleft lip and/or palate and congenital heart disease.

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John Graham, MD, brought case 3 to our attention. M. Michael Cohen, DDS, reviewed the manuscript.

References

1. Vanderwoude A: Fistula labii inferioris congenital and its association with cleft lip and palate. *Am J Hum Genet* 6:244-256, 1954.

2. Gorlin RJ, Sedano HO, Cervenka J: Popliteal pterygium syndrome: A syndrome comprising cleft lip-palate, popliteal and intercrural pterygia, digital and genital anomalies. *Pediatrics* 41:503-509, 1968.

3. Hecht F, Jarvinen JM: Heritable dysmorphic syndrome with normal intelligence. *J Pediatr* 70:927-935, 1967.

4. Gorlin RJ, Psaume J: Orodigitofacial dysostosis: A new syndrome. *J Pediatr* 61:520-530, 1962.

5. Cervenka J, Gorlin RJ, Anderson VE: The syndrome of pits of the lower lip and cleft lip and/or palate: Genetic considerations. *Am J Hum Genet* 19:416-432, 1967.

6. Csiba A: Bilateral connate fistula of the lower lip. *Oral Surg* 22:226-230, 1966.

7. Michaelides AC, Hay RJ, Wells RS: Congenital sinuses of the lower lip. *Trans St Johns Hosp Dermatol Soc* 61:82-86, 1975.

8. Everett FG, Wescott WB: Commissural lip pits. *Oral Surg* 14:202-209, 1961.

9. Baker BR: Pits of the lip commissures in Caucasoid males. *Oral Surg* 21:56-60, 1966.

10. Schneider EL: Lip pits and congenital absence of second premolars: Varied expression of the lip pits synrome. *J Med Genet* 10:346-349, 1973.

11. Hilgenreiner H: Die angeborenen fitel Bzw schleimhauttaschen der unterlippe. *Dtsch Z Chir* 188:273-309, 1924.

12. Ludy JB, Shirazy E: Concerning congenital fistulae of the lips; their mooted significance; review of the literature; and report of family with congenital fistulae of the lower lip. *N Int Clin* 3:75-88, 1938.

13. Pohl L: Letter. *Dent Prac* 7:112, 1956.

14. Calnan JS: Congenital double lip: Record of a case with a note on the embryology. *Br J Plast Surg* 5:197-202, 1952.

15. Fraser GR, Calnan JS: Cleft lip and palate: Seasonal incidence, birth weight, birth rank, sex, site, associated malformations and parental age. *Arch Dis Child* 36:420-423, 1961.

16. Baxter H: Congenital fistulas of the lower lip. *Am J Orthod Oral Surg* 25:1002-1007, 1939.

17. Roselli D, Gulienetti R: Ectodermal dysplasia. *Br J Plast Surg* 14:190-240, 1961.

18. Soricelli DA, Bell L, Alexander WA: Congenital fistulas of the lower lip. *Oral Surg* 21:511-516, 1966.

19. Newman Z, Shulman J: Congenital sinuses of the lower lip. *Oral Surg* 14:1415-1420, 1961.

20. Test AR, Falls HF: Dominant inheritance of cleft lip and palate in five generations. *J Oral Surg* 5:292-297, 1947.

21. Shah CV, Pruzansky S, Harris WS: Cardiac malformations with facial clefts: With observations on the Pierre Robin syndrome. *Am J Dis Child* 119:238-244, 1970.

22. Boesen I, Melchior JC, Terslev E, et al: Extracardiac congenital malformations in children with congenital heart diseases. *Acta Paediatr*, suppl 146, 1963, pp 28-33.

23. Okada R, Johnson D, Lev M: Extracardial malformations associated with congenital heart disease. *Arch Pathol* 85:649-657, 1968.

24. Warbrick JG, McIntyre JR, Ferguson AG: Remarks on the aetiology of congenital bilateral fistulae of the lower lip. *Br J Plast Surg* 4:254-262, 1952.

Topically Applied Testosterone and Phallic Growth

Its Effect in Male Children With Hypopituitarism and Microphallus

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• Topical application of 5% testosterone cream for 21 days resulted in enlargement of the penis to normal size for age in five boys with normal XY karyotype who had microphallus and hypopituitarism. In four patients, testosterone cream was applied locally to the penis and in one to an area of skin in the right axilla. Serum testosterone values rose from infantile levels before the start of therapy to normal adult male levels on the last day of treatment. All patients were receiving human growth hormone at the time of therapy with testosterone. No additional acceleration of linear growth and no advance in osseous maturation occurred during or after treatment. Application of testosterone locally for this brief period is a safe, effective, and simple means of stimulating phallic growth. Our findings suggest that topical testosterone causes penile growth predominantly through its systemic action.

(*Am J Dis Child* 134:296-298, 1980)

Previous reports have documented the presence of microphallus in boys with hypopituitarism and have indicated the beneficial effects on phallic growth of systemic testosterone therapy.[1,2] Phallic growth probably depends on adequate tissue levels of dihydrotestosterone, with testosterone being converted to dihydrotestosterone in the target tissue. Immergut et al[3] in a preliminary report suggested that the observed effects of topically applied testosterone were local rather than systemic. Subsequent reports[4,5] were consistent with regard to the efficacy of topical testosterone, and suggested that the observed increase in phallic size was due to the systemic action of testosterone. We studied the effect of topical application of testosterone cream in five boys with micropenis and hypopituitarism.

SUBJECTS AND METHODS

All subjects were treated with 5% testosterone propionate in hydrophilic ointment USP. Average dosage was between 2.5 and 4.0 mg of testosterone (50 to 75 mg of ointment) applied three times a day for three weeks, on an approximate area of 9 sq cm. In four patients (1 through 4), the ointment was applied directly to the phallus, and in one patient (5) to his right axilla. Total treatment dose for each patient was less than 300 mg.

Linear growth, bone age, penile size, and plasma testosterone concentrations were determined prior to treatment, three to four hours after the final application, and six to 12 months after the conclusion of therapy. Penile size was determined by the same observer according to Schonfeld's method.[6] Height was measured with a stadiometer.

Bone age was determined on the left hand and wrist using the method of Greulich and Pyle.[7] Plasma testosterone concentrations were measured by radioimmunoassay at Bio-Science Laboratories, St Louis.

Five patients were studied. Informed consent was obtained from the parents of all patients. Patients 1 and 2, aged 6 years and 8 months and 11 years and 2 months, respectively, had panhypopituitarism and microphallus and were receiving adequate replacement therapy of growth hormone (GH), cortisol, and thyroxine. Patients 3 and 4, aged 2 years and 6 months and 7 years and 7 months, respectively, had isolated GH deficiency and microphallus and were receiving treatment with GH at the time of this study. Patient 5, aged 3 years and 8 months, had GH and adrenocorticotropic hormone deficiency and was receiving therapy with GH. All patients had severe hypoglycemic episodes in early infancy, presumably due to hormonal deficiencies.

RESULTS

As can be seen in the Figure and in the Table, the penis increased in size after therapy to within the normal range for age in all patients except for patient 4. This patient was extremely

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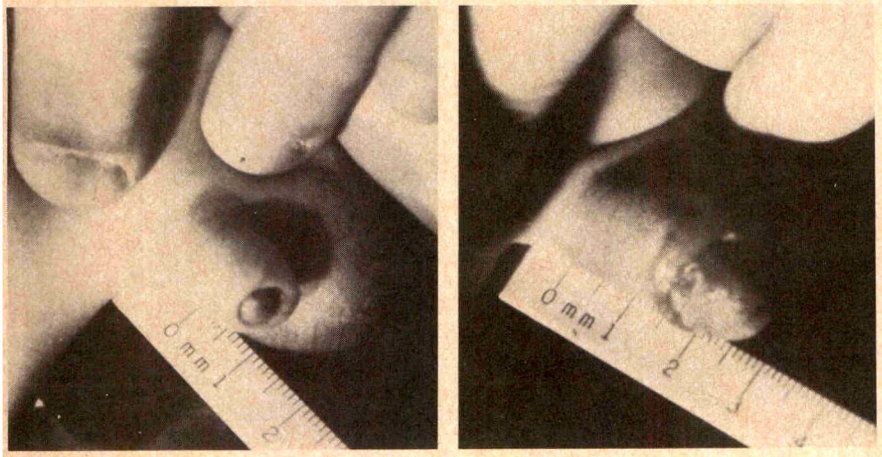
short. His penis doubled in size during treatment and became appropriate for his height and bone age, but not for his chronological age.

The desired effect was obtained at the end of three weeks of treatment in all four patients in whom testosterone was applied directly to the penis. No further change in phallic size was noticed during the follow-up period (Table). However, in patient 5, in whom testosterone was applied (in similar dosage) to his right axilla, only partial response was noted at the end of three weeks of treatment (Table), namely an increase from 1.8 to 3.0 cm in length. The penis continued to increase in size during the next three weeks after treatment had been discontinued until it reached a length of 4.0 cm, which was more than double the initial size and similar to the increase in size in the other patients. No further change in penile size was noted in this patient after the sixth week.

No change in linear growth velocity was noted in any of the patients either during the three-week period of treatment or during the follow-up period. Similarly, bone age and height age did not advance disproportionately (Table). Undesirable side-effects were minimal. In only two of the four patients who had testosterone applied directly to the penis did three to four downy pubic hairs develop. These disappeared shortly after cessation of treatment. Facial or axillary hair did not develop. Patient 5 was noted to have a slight increase in local pigmentation in his right axilla, where topical testosterone was applied. This pigmentation gradually disappeared during the three weeks after treatment was stopped. In none of the patients did acne or deepening of the voice develop. By history, daily activity and sleep patterns were not altered.

Plasma testosterone concentration was within the prepubertal level for all the patients before treatment (< 20 ng/mL) and rose during the treatment to the normal adult male range (276 to 960 ng/mL), including patient 5, whose testosterone level reached 573 ng/mL on the last day of treatment.



Genitalia of patient 5 before (left) and after (right) treatment.

COMMENT

Children with microphallus who may benefit from administration of topical or systemic testosterone fall into two major categories: those with urologic abnormalities, including hypospadius and penile cordee, and those with idiopathic hypopituitarism in whom there is usually a deficiency of hypothalamic-hypophysiotropic hormones. One should be aware that patients in the first group may have

Clinical Data of Patient Population and Results of Topically Applied Testosterone Cream on Penile Growth, Bone Age, and Serum Testosterone Levels

	Patient				
	1	2	3	4	5*
Diagnosis	GH/ACTH/TSH† deficiency; microphallus	GH/ACTH/TSH deficiency; microphallus	Isolated GH deficiency; microphallus	Isolated GH deficiency; microphallus	GH and ACTH deficiency; microphallus
Chronologic age, yr/mo	6/8	11/2	2/6	7/7	3/8
Height age, yr/mo	5/2	8/7	1/5	2/10	1/3
Bone age, yr/mo, before treatment	5/6	10/0	0/6	3/6	1/6
ΔBA/ΔCA‡	9/12	0/6	15/15	6/9	0/3
Penile length					
Before treatment, cm	3.0	2.5	1.8	1.0	1.8
After treatment, cm	5.0	7.5	4.0	2.0	3.0
During follow-up, cm	Same	Same	Same	Same	4.0
Normal for age, cm§	4.9-7.3	5.3-8.1	3.9-6.6	5.0-7.4	4.5-6.7
Plasma testosterone, ng/mL					
Before	< 20	< 20	< 20	< 20	< 20
Last day of treatment	276	960	740	. . .	573

*Axillary application of testosterone cream.
†GH indicates growth hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone.
‡ΔBA/ΔCA indicates advance in bone age over change in chronological age, in months.
§Tenth to 90th percentile.

partial or complete end-organ resistance to testosterone. Although GH may play a permissive role in promoting phallic growth, most evidence suggests that dihydrotestosterone is the primary determinant of phallic size. The knowledge that microphallus due to hormonal deficiency will respond to exogenous testosterone can be reassuring to parents, the patient, and the physician.

Two methods of testosterone administration have been evaluated: topical and intramuscular.[1-5] Each method has advantages. Lovinger and co-workers[2] described three patients similar to those in the present study whose phallic size responded favorably to treatment with 25 to 30 mg/mo of testosterone enanthate in oil given intramuscularly during a three-month period. No increase in skeletal maturation was observed, although a transient increase in growth velocity was noted. Guthrie and co-workers[1] used similar doses of testosterone cypionate intramuscularly in four patients. Although a transient acceleration in both linear growth and osseous maturation was observed in these patients initially, two years after cessation of therapy the rate of skeletal maturation and linear growth seemed to be normal. However, it should be pointed out that intramuscular testosterone in less experienced hands is not without risk to the patient. Advancement of osseous maturation out of proportion to increments in linear height may occur, as well as the onset of secondary sexual characteristics, including public, facial, and axillary hair and deepening of the voice.

Several reports have suggested the efficacy of topical testosterone when applied to the microphallus.[1,4,5] Immergut and co-workers[3] suggested that the effects of topical testosterone were local rather than systemic; however, Jacobs et al[5] found that elevated serum testosterone levels in two of their three patients supported the view that the observed effects of topical therapy are due to increased circulating testosterone levels. Further evidence that this is indeed the case was obtained in patient 5, in whom phallic growth and elevated serum testosterone levels occurred when testosterone was applied to the axilla.

Although it has been suggested that there may be psychological disadvantages to this form of therapy, the favorable response to short-term topical testosterone administration in all of the patients in this report suggests that this form of therapy may be easier to manage than intramuscular injections. There was no observed acceleration in linear growth or osseous maturation, the medication is easy to apply, the desired effect is achieved in a short time, and, finally, the cost of this form of therapy is substantially less than that of intramuscular treatment.

Elevated serum testosterone levels were observed in four of the five patients in this study. Although we do not have supporting data, we hypothesize that the repeated topical application of testosterone and the slower absorption by this route of administration results in more sustained blood levels of the hormone during the course of therapy. It is possible that this route of administration more nearly mimics the physiologic elevations of testosterone observed by Forest and co-workers[8] in the male neonate.

Recently, Read and co-workers[9] studied the effect of topical application of dihydrotestosterone in prepubertal rats. Their observations suggest that dihydrotestosterone may be an even safer form of therapy, since significant penile growth occurred in these animals without elevated plasma levels of the hormone.

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References

1. Guthrie RD, Smith DW, Graham CB: Testosterone treatment for micropenis during early childhood. *J Pediatr* 83:247-252, 1973.

2. Lovinger RD, Kaplan SL, Grumbach MM: Congenital hypopituitarism associated with neonatal hypoglycemia and microphallus: Four cases secondary to hypothalamic hormonal deficiency. *J Pediatr* 87:1171-1181, 1975.

3. Immergut M, Boldus R, Yannone E, et al: The local application of testosterone cream to the prepubertal phallus. *J Urol* 150:905-906, 1971.

4. Darby CW, Vanderschvern-Looeweyckx M, Laurance BM: Testosterone cream; Use or abuse? *Lancet* 2:598, 1974.

5. Jacobs SC, Kaplan GW, Gittes RF: Topical testosterone therapy for penile growth. *Urology* 6:708-710, 1975.

6. Schonfeld WA: Primary and secondary sexual characteristics. *AMA J Dis Child* 65:535-549, 1943.

7. Greulich WW, Pyle SI: *Radiographic Atlas of Skeletal Development of the Hand and Wrist.* Stanford, Calif, Stanford University Press, 1959.

8. Forest MG, Sizonenko PC, Cathiard AM, et al: Hypophyso-gonadal function in humans during the first year of life. *J Clin Invest* 53:819-828, 1974.

9. Read BP, Lloyd JW, Eisenberg J, et al: Adrenergic effects of testosterone and dihydrotestosterone applied topically to the rat phallus. *Surg Forum* 27:581-583, 1976.

Brachial Plexus Neuropathy

Three Cases in Children

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Brachial plexus neuropathy is an acute neurologic disorder characterized by pain, weakness, and atrophy of the muscle groups affected. Although well documented in the adult literature, relatively few cases have been reported in children. Despite the lack of knowledge concerning its etiology, and lack of an effective therapy, the long-term prognosis is excellent. It is perhaps for these reasons that spinal fluid analysis is not routinely performed during the acute phase of this illness. An evaluation of the clinical course of three children, together with epidemiologic data, suggests that early lumbar punctures and an extensive search for an infecting viral agent, notably coxsackievirus B, are warranted.

(*Am J Dis Child* 134:299-300, 1980)

Brachial plexus neuropathy (BPN) is a well-documented clinical entity, which is characterized by the sudden onset of pain, usually about the neck, shoulder, or upper arm, and is closely followed by weakness and later, depending on the severity of the illness, by atrophy of the muscle groups involved. Many cases have been associated with the injection of foreign sera,[1] routine immunizations,[2-4] viral illnesses,[5,6] or desensitizing injections,[7] but the exact nature of the disorder remains obscure. In addition, a number of families have been described whose affected members exhibit recurrent episodes of BPN, clinically indistinguishable from those cases that appear sporadically.[8]

Although the literature documents the occurrence of BPN among children, such reports have been relatively infrequent.[3,9-11] We here report three additional cases, two of which appeared within days of each other, concurrent with a local enterovirus epidemic.

REPORT OF CASES

CASE 1.—A 2-year, six-month-old, left-handed boy had had an upper respiratory infection for three days prior to the onset of specific symptoms. When fever up to 40 °C developed, he was taken to an area hospital where a diagnosis of bilateral otitis media and pharyngitis was made and where ampicillin oral suspension was prescribed. The next day, Aug 30, 1976, he refused to use his left arm and was hospitalized for evaluation. There had been no recent trauma or injections of any sort and his immunizations were complete. His birth history was unremarkable and development, thus far, had been normal. There was no family history of BPN or other forms of neurologic disease.

On physical examination, his temperature was normal and his height and weight were at the ninth and 75th percentiles, respectively. His head was held tilted to the left, and the left arm was adducted, internally rotated, and extended at the elbow. The left scapula was not winged. No appreciable voluntary movement of the left shoulder or flexion of the elbow could be elicited. Finger movements and grasp of the left hand were intact, as were pain, touch, position, and vibratory sensations. The left biceps reflex was reduced (+1), but all other reflexes were normal. Results of the complete blood cell count (CBC), urinalysis, tine test, sedimentation rate, blood culture, monospot test, serum lead and free erythrocyte protoporphyrin levels, antinuclear antibody activity and lupus erythematosus preparation, serum creatinine phosphokinase level, protein electrophoresis, and roentgenograms of the cervical spine, chest, and left arm were either normal or negative. The CSF obtained on the second hospital day showed nine WBCs per cubic millimeter (two neutrophils, seven lymphocytes), a glucose level of 54 mg/dL, and a protein value of 8 mg/dL. No viruses were isolated from the nasopharynx. Five days after the onset of symptoms, some improvement in the weakness was noted. One month later, functional recovery was complete. He was able to raise his left hand above his head and to pull himself up from a standing position. When examined one year later, the child had completely recovered.

CASE 2.—A 10-month-old male infant had been well until approximately five days before admission in July 1977 when mild symptoms of an upper respiratory infection developed. Three days after the onset of illness, intermittent fever was noted. He awoke that night crying, and manipulation of the left arm seemed to cause pain. The next morning, he was unable to move the left arm, and was hospitalized for evaluation. His history and family history were unremarkable.

When examined, his temperature was 38.6 °C. Physical findings relating to the left upper extremity were nearly identical to those in case 1, except that winging of the left scapula was present. In addition, the left hand was noticeably weaker than the right hand, and the left biceps, triceps, and brachioradialis reflexes were absent. Sensation to pinprick over the left arm and shoulder was intact. Other important physical findings included mild nasal congestion, hyperemia of both tympanic membranes, and a 2 × 1.5-cm area of hyperemia over both shoulders. A laboratory evaluation similar to that performed in case 1 showed no abnormalities. A lumbar

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puncture (LP) performed on the third hospital day showed one WBC per cubic millimeter, a glucose level of 65 mg/dL, and protein value of 52 mg/dL. By the fifth hospital day, some voluntary muscle activity had returned to the affected extremity. When seen again about six months later, he had completely recovered, with no residual weakness or atrophy of the left shoulder, arm, or hand noted.

Case 3.—Three days prior to admission on June 27, 1977, a 7-year, 6-month-old, right-handed boy had pain along the left side of his neck that his mother attributed to trauma sustained while playing tag the previous day. He also felt warm so acetaminophen (Tylenol) was given. Two days later, he remained in bed stating that he did not feel well. By midday, he was unable to lift his left arm. The past history and family history were again noncontributory.

When examined, he was complaining of left neck and shoulder pain. His temperature was 39 °C. Notable physical findings included nuchal rigidity and a positive Kernig's sign. The left shoulder and arm were involved in a manner similar to the previous two cases except that winging of the scapula was not present, and left-hand function was not impaired. The CBC showed 10,700 WBCs per cubic millimeter, with 63% neutrophils, 11% bands, 13% lymphocytes, 11% monocytes, and 2% eosinophils. The CSF on admission showed an opening pressure of 17 cm H_2O, 53 WBCs per cubic millimeter (69% neutrophils, 31% lymphocytes, and no RBCs), a glucose level of 101 mg/dL, and a protein value of 23 mg/dL. No organisms were present on the smear, and the culture was negative. The remainder of his laboratory evaluation was unremarkable.

On the first hospital day, his temperature increased to 40.5 °C. After the second day, his temperature returned to normal, and the nuchal rigidity resolved. Atrophy of the left shoulder became noticeable after two weeks. Throughout the hospitalization, he complained intermittently of pain in the left shoulder and arm. Electrostimulation and ultrasound treatments were given weekly. After two months, some shoulder abduction and elbow flexion against gravity had returned. When seen at six months and again one year after the onset of illness, atrophy of the left deltoid, biceps, and spinatii muscles was still present. He was able to abduct the left arm only with gravity eliminated, and he could flex the elbow but not the shoulder against gravity and minimal resistance. The left biceps jerk was reduced as compared with the right. Throughout the interim period, no sensory loss or pain had been noted.

COMMENT

The clinical features presented by these three cases are fairly characteristic and represent the most common form of BPN, ie, unilateral involvement of the motor fibers arising from spinal cord segments C-5, C-6, and C-7. The data of Tsairis et al[10] indicate that in 89% of cases, recovery is complete after three years, regardless of the extent or severity of the initial involvement.

Elevation of CSF protein is known to occur in some cases of BPN, but the modest cellular reaction observed in two of our patients is noteworthy. Pleocytosis was demonstrated in only two of the patients cited by the literature we reviewed. In one instance, the LP was performed one week after inoculation with a combination of diphtheria and tetanus toxoids and pertussis vaccine.[3] The other patient had infectious mononucleosis, but the interval between the onset of illness and the LP was not specified.[10] In all other cases of BPN, the CSF when examined yielded normal results. The "customary" delay in performing an LP beyond the acute phase of this disease (beyond two weeks after onset), may explain the apparent lack of abnormalities. Three days after initial symptoms, case 3 showed both a mixed cellular reaction and physical signs of meningeal irritation. Finding nine WBCs per cubic millimeter in the CSF of case 1, six days after the onset of illness, is also abnormal. The CSF in case 2 showed increased protein content but no pleocytosis, but it should be noted that the LP was performed eight days after the initial symptoms.

In cases 1 and 2, the onset of neuropathy followed what seemed to be a viral upper respiratory tract infection, and although symptoms in case 3 were antedated by trauma (probably unimportant), the findings of fever, malaise, a modest peripheral leukocyte reaction with a left shift, and inflammatory cells in the CSF strongly implicate an infectious etiology. Of the cases of Tsairis et al,[10] 25% were associated with upper respiratory infection or influenza-like illness. Coxsackievirus B is suggested as playing a causative role by the epidemiologic study of Bardos and Somodska.[5] In the absence of careful viral studies, it is not possible to document an etiologic association between coxsackievirus B and BPN in our patients. However, during the months of June through September 1977, a community-wide epidemic of coxsackievirus B (particularly B2) occurred in association with several documented cases of aseptic meningitis at the Children's Hospital National Medical Center nearby (H. W. Kim, MD, oral communication). The concurrence of these phenomena, though far from conclusive, are suggestive that some as yet undetermined connection exists; and they imply that a more aggressive approach toward CSF examination in the acute phase of BPN, along with the addition of viral studies from many sites, including the CSF, may shed light on the etiologic factor of this perplexing and fairly common syndrome.

Nonproprietary Name and Trademarks of Drug

Ampicillin—*Alpen, Amcill, Omnipen, Penbritin, Polycillin, Principen.*

References

1. Woolling KR, Rushton JG: Serum neuritis: Report of two cases and brief review of the syndrome. *Arch Neurol Psychiatr* 64:568-573, 1950.
2. Miller HG, Stanton JB: Neurological sequelae of prophylactic inoculation. *Q J Med* 23:1-27, 1954.
3. Matin GI, Weintraub MI: Brachial neuritis and seventh nerve palsy: A rare hazard of DPT vaccination. *Clin Pediatr* 12:506-507, 1973.
4. Weintraub MI, Chia DTS: Paralytic brachial neuritis after swine flu vaccination. *Arch Neurol* 34:518, 1977.
5. Bardos V, Somodska V: Epidemiologic study of a brachial plexus neuritis outbreak in northeast Czechoslovakia. *World Neurol* 2:973-979, 1961.
6. Watson P, Ashby P: Brachial plexus neuropathy associated with infectious mononucleosis. *Can Med Assoc J* 114:766-767, 1976.
7. Wolpow ER: Brachial plexus neuropathy associated with desensitizing antiallergy injections. *JAMA* 234:620-621, 1975.
8. Dunn HG, Daube JR, Gomez MR: Heredofamilial brachial plexus neuropathy in childhood. *Dev Med Child Neurol* 20:28-46, 1978.
9. Magee KR, DeJong RN: Paralytic brachial neuritis: Discussion of clinical features with review of 23 cases. *JAMA* 174:1258-1262, 1960.
10. Tsairis P, Dyck PJ, Mulder DW: Natural history of brachial plexus neuropathy: Report on 99 patients. *Arch Neurol* 27:109-117, 1972.
11. Shaywitz BA: Brachial plexus neuropathy in childhood. *J Pediatr* 86:913-914, 1975.

Necrotizing Fasciitis After Neonatal Circumcision

Jeffrey R. Woodside, MD

• A 6-day-old infant had extensive necrotizing fasciitis involving most of the abdominal wall develop after circumcision with a Plastibell device (Hollister, Inc). He survived this life-threatening infection after vigorous cardiovascular support, antibiotic therapy, and aggressive surgical debridement. The diagnosis, bacteriology, and management of necrotizing fasciitis are briefly discussed. The technical aspects and complications of Gomco (Gomco Surgical Manufacturing Corp) and Plastibell circumcision are compared. Strangulation and devitalization of the prepuce is invariably associated with Plastibell circumcision, and it may render neonates circumcised by this technique more susceptible to serious wound infection.

(*Am J Dis Child* 134:301-302, 1980)

Neonatal circumcision is the most commonly performed surgical procedure in the United States today. Although considered a minor operation, reported complications include infection, hemorrhage, loss of penile skin, laceration of penile or scrotal skin, injury to the glans, urethral fistula, urinary retention, staphylococcal scalded skin syndrome, concealed penis, and retained Plastibell rings (Hollister, Inc).[1-6] The experience with a newborn who had extensive necrotizing fasciitis of the abdominal wall develop after circumcision is the subject of this report. Necrotizing fasciitis has seldom been described in children, and to my knowledge, it has been reported only twice in neonates.[7-8]

REPORT OF A CASE

A 2.6-kg male infant was born by normal vaginal delivery after 39 weeks' gestation. He was circumcised without incident by the Plastibell technique at age 3 days. Two days later, his mother noticed slight penile swelling and a small amount of blood and pus on the diapers. Later in the day, the penis and scrotum turned black-purple in color. The Plastibell was removed at another hospital, and he was transferred to our institution.

He was lethargic, and he appeared acutely ill. His rectal temperature was 35.3 °C, his heart rate was 132 beats per minute, his respiratory rate was 40/min, and his systolic blood pressure was 40 mm Hg. Petechiae and multiple, 5-mm, flat, black-purple lesions covered the trunk, arms, and legs. The skin of the shaft of the penis and part of the scrotum was necrotic. Induration and slight erythema of the skin of the abdominal wall extended from the inguinal areas to the level of the umbilicus. The hemoglobin level was 14 g/dL; hematocrit, 42%; platelet count, 7,500/cu mm; and WBC count, 26,700/cu mm, with 36% neutrophils, 19% band forms, 39% lymphocytes, 4% monocytes, and 2% eosinophils. The prothrombin time was 14 s (control, 11 s); partial thromboplastin time, 40 s; fibrinogen level, 86 mg/dL; creatinine clearance, 0.9 mg/dL; BUN level, 37 mg/dL; and total bilirubin level, 8.5 mg/dL. Lumbar puncture yielded normal CSF. Gram's stain of the contents from several of the skin lesions showed Gram-positive cocci.

His condition was treated with parenteral fluids, fresh frozen plasma, human antihemophilic factor (cryoprecipitate) and platelet concentrates. Parenteral nafcillin sodium, penicillin G potassium, chloramphenicol sodium succinate, and kanamycin sulfate were given.

The nonviable skin of the entire penile shaft was surgically debrided; the glans penis and corpora cavernosa appeared healthy. Two incisions were started at the base of the penis and carried superiorly across the suprapubic area. The underlying subcutaneous tissue and superficial fascia were necrotic. These incisions were then extended superiorly into the flanks before viable subcutaneous tissue was encountered. The resultant large, V-shaped flap was extensively undermined and debrided. Multiple fasciotomies of the external oblique aponeurosis were performed, and the underlying muscles were healthy. The wounds were packed loosely with moist dressings. Postoperatively, his cardiovascular status rapidly improved, and sepsis and disseminated intravascular coagulation resolved.

Gram's stain of the surgically excised subcutaneous tissue showed a mixture of Gram-positive and Gram-negative rods and cocci. No organisms grew in an anaerobic culture of this same tissue, and the aerobic culture showed a combination of growths of coagulase-positive *Staphylococcus aureus*, *S epidermidis*, diphtheroids, nonhemolytic streptococcus, and α-hemolytic streptococcus. *Clostridium perfringens* was cultured from the necrotic penile tissue but not from the subcutaneous tissue. Culture of the contents of the septic skin emboli was sterile. A *Micrococcus* species was grown from a culture of the blood.

The extensive abdominal wound was treated with wet-to-dry dressings for further debridement. Granulation tissue was present in most of the wound after one week of therapy, and only the apex of the abdominal skin flap and a small area of the scrotum were nonviable (Fig 1). Ten days after admission, the wounds were surgically debrided of all remaining necrotic tissue, and the abdominal wound was closed primarily (Fig 2). The scrotum was closed loosely, and a split-thickness skin graft was placed around the penile shaft. The abdominal and scrotal wounds were well healed two months later (Fig 3). Minor scar revisions will be necessary, but the functional and cosmetic results should be excellent.

COMMENT

Necrotizing fasciitis is a rapidly spreading bacterial infection producing edema, necrosis, and partial liquifaction of the subcutaneous fat, superficial fascia, and superficial layer of the deep fascia. It most frequently involves the extremities and abdominal wall, and it may occur after surgery or after relatively minor trauma such as abrasions, cuts, or insect bites.[9] Meleny[10] first described 20 patients with this entity and cultured a hemolytic streptococcus from each. Culture results in more recent reports have usually demonstrated a combination of anaerobic and facultative anaerobic bacteria.[9,11] Successful culture of these bacteria requires meticulous technique, and failure of the more fastidious organisms to grow is not unusual. Patients with necrotizing fasciitis commonly have sepsis, disseminated intravascular coagulation, and hypotension, as in this patient.

Consideration of this disease in the appropriate clinical setting and a high index of suspicion are required to detect the early skin changes of minimal erythema and poorly demarcated induration. Initial treatment must

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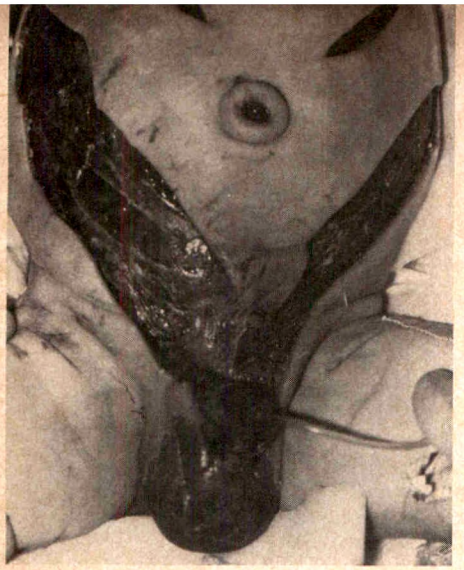

Fig 1.—Abdominal wall and genitalia one week after extensive debridement. Apex of abdominal flap and small scrotal area are nonviable. Fasciotomies of right external oblique aponeurosis are demonstrated.

Fig 2.—Primary closure of abdominal wounds. Split-thickness skin grafts have been applied to penile shaft and small, upper abdominal incisions.

Fig 3.—Well-healed abdominal and scrotal wounds two months after closure. Moderate contraction of suprapubic and penile scars has occurred.

consist of cardiovascular stabilization and parenteral antibiotics effective against a broad spectrum of aerobic and anaerobic organisms. Giuliano and associates[11] recommend initial antibiotic treatment with penicillin, a penicillinase-resistant penicillin, gentamicin or tobramycin, and clindamycin or chloramphenicol. The most important aspect of therapy is surgical debridement and excision of all involved fascia and subcutaneous tissue. The reported mortality for necrotizing fasciitis ranges from 13% to 60%, with better survival after more radical surgical treatment.

Neonatal circumcision is usually performed with either the Plastibell device or the Gomco circumcision clamp (Gomco Surgical Manufacturing Corp). The Gomco clamp seals together the skin and mucosal surfaces of the prepuce by briefly applied extrinsic pressure. The Plastibell technique crushes the prepuce between a suture and an underlying bell, which drops off in five to eight days.

Gee and Ansell[12] reviewed the complications of 5,521 neonatal circumcisions performed during a ten-day period. The Gomco and Plastibell techniques were each used in approximately one half of the patients. The cumulative complication rate was 0.2%, with no significant differences between the two techniques for the various complications, except for infection. Wound infection occurred in 0.14% of the patients circumcised with the Gomco, and 0.72% with the Plastibell. All infections were initially managed with local cleansing, and each infection after the Gomco circumcision resolved promptly. However, 20% of those infected after Plastibell circumcision had fever and irritability, which resolved only after the antibiotic therapy. The Plastibell technique strangulates the prepuce and produces devitalized tissue that might be more susceptible to serious infection. The more loosely approximated prepuce after the Gomco technique would seem to permit ready egress of any purulence from between preputial layers. Thus, a wound infection of the circumcision site would tend to be locally contained.

The Committee on Fetus and Newborn of the American Academy of Pediatrics has stated that there are no valid medical indications for circumcision in the neonatal period. Nevertheless, many parents will still desire to have their male infants circumcised. Therefore, each physician performing circumcisions should be mindful that "circumcision is a surgical procedure that requires careful aseptic technique, systematized postoperative observation, and evaluation after discharge from the hospital."[13] Serious and potentially life-threatening infections after circumcision of the newborn occur more frequently after Plastibell circumcision.[12,14] This evidence suggests that Gomco circumcision is the preferred technique.

References

1. Sussman SJ, Schiller RP, Shashikumar VL: Fournier's syndrome: Report of three cases and review of the literature. *Am J Dis Child* 132:1189-1191, 1978.
2. Shulman J, Ben-Hur N, Neuman Z: Surgical complications of circumcision. *Am J Dis Child* 107:149-154, 1964.
3. Berman W: Urinary retention due to ritual circumcision. *Pediatrics* 56:621, 1975.
4. Annunziato D, Goldblum LM: Staphylococcal scalded skin syndrome: A complication of circumcision. *Am J Dis Child* 132:1187-1188, 1978.
5. Trier WC, Drach GW: Concealed penis: Another complication of circumcision. *Am J Dis Child* 125:276-277, 1973.
6. Datta NS, Zinner NR: Complication from Plastibell circumcision ring. *Urology* 9:57-58, 1977.
7. Wilson HD, Haltalin KC: Acute necrotizing fasciitis in childhood: Report of 11 cases. *Am J Dis Child* 125:591-595, 1973.
8. Weinberger M, Haynes RE, Morse TS: Necrotizing fasciitis in a neonate. *Am J Dis Child* 123:591-594, 1972.
9. Tehrani MA, Ledingham IM: Necrotizing fasciitis. *Postgrad Med J* 53:237-242, 1977.
10. Meleny FL: Hemolytic streptococcus gangrene. *Arch Surg* 9:317-364, 1924.
11. Giuliano A, Lewis F, Hadley K, et al: Bacteriology of necrotizing fasciitis. *Am J Surg* 134:52-57, 1977.
12. Gee WF, Ansell JS: Neonatal circumcision: A ten-year overview: With comparison of the Gomco clamp and the Plastibell device. *Pediatrics* 58:824-827, 1976.
13. Thompson HC, King LR, Knox E, et al: Report of the ad hoc task force on circumcision. *Pediatrics* 56:610-611, 1975.
14. Kirkpatrick BV, Eitzman DV: Neonatal septicemia after circumcision. *Clin Pediatr* 13:767-768, 1974.

The George Armstrong Award Lecture

Are We in the Midst of a Revolution?

John H. Kennell, MD

In his book *The Structure of Scientific Revolutions*, Thomas Kuhn wrote:

> Normal science . . . is predicated on the assumption that the scientific community knows what the world is like. Much of the success of the enterprise derives from the community's willingness to defend that assumption, if necessary at considerable cost. Normal science, for example, often suppresses fundamental novelties because they are necessarily subversive of its basic commitments, but . . . the very nature of normal research ensures that novelty shall not be suppressed for very long.
>
> Major turning points in [the] scientific development [of the physical sciences] are associated with the names of Copernicus, Newton, Lavoisier, and Einstein. Each of them necessitated the community's rejection of one time-honored scientific theory in favor of another incompatible with it. They transformed the world in which scientific work was done. Such changes, together with the controversies that almost always accompany them, are the defining characteristics of scientific revolutions.[1]

For millions of years human beings had watched the stars move across the heavens, apples fall from trees, and wood burn. Ever since a major turning point in scientific knowledge was reached by investigators who studied and considered these natural events very carefully, we have had a different view of these phenomena. Over a similar span of time, human beings have observed the birth of babies and their nursing and nurturing until they were ready to lead independent lives. There have been an accelerating number of powerful influences on these vital human events, eg, birth and death in the hospital, or the myriad of shifting and changing child rearing theories. An example of the latter was the theory of John Watson in the late 1920s. He advocated a rigid approach to child rearing and advised parents to impose strict schedules on their children for feeding, toileting, and almost every other activity, including loving. He advised mothers not to kiss their children, because kissing interferes with digestion and deranges the glandular system. He advised "never hug and kiss them, never let them sit in your lap . . . kiss them once on the forehead when they say goodnight. Shake hands with them in the morning."[2] Have factors affecting human development, such as the child rearing theory of the month, received the scrutiny, investigation, and evaluation that has been directed to the stars and planets, to the principles of chemistry, physics, and mathematics?

Patterns of family life, human development, and the customs surrounding the two major life events, birth and death, were modified slowly and gradually until the start of the revolutionary industrial and social changes that began about the time George Armstrong opened his clinic for poor sick children in 1769. As a result of technologic progress and the remarkable advances in pediatrics and obstetrics, we all know that many more babies and mothers survive, but we are faced with an overwhelming array of individual, family, and societal problems.

Is it possible that we have discarded or overlooked treasures of evolutionary wisdom for human development in the rush of progress? The side effects on infants and parents of most of the innovations of the last 200 years have never been studied scientifically.

Are we in the midst of a scientific revolution that can blend evolutionary patterns from the past with advances in the future? Are we suppressing novelties, either old or new, that do not fit with our normal science, our present day US view of what the world is like?

Today we honor one of the major innovators in medicine, George Armstrong. He was suppressed and unappreciated because he had a novel solution to the problems of sick children. Earlier in this century, Sir George Still called the opening of Armstrong's dispensary "the most important step ever taken [in England] towards the care of sick children."[3] The effects of this physician's efforts

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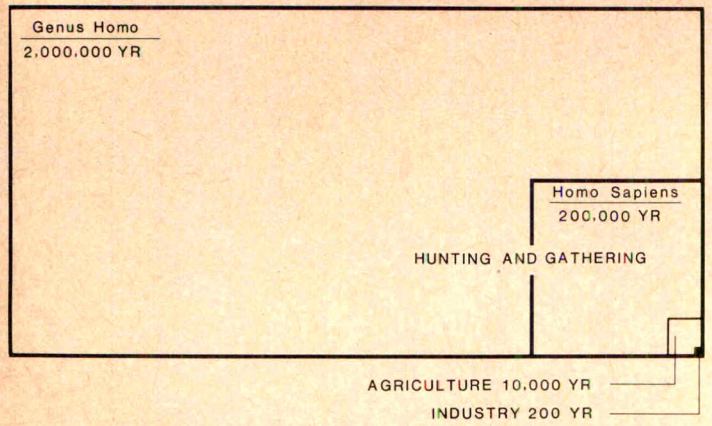

Fig 1.—Relatively brief periods that humans have lived in agricultural and industrial mode of existence compared to long duration as hunters and gatherers. (Courtesy of Betsy Lozoff.)

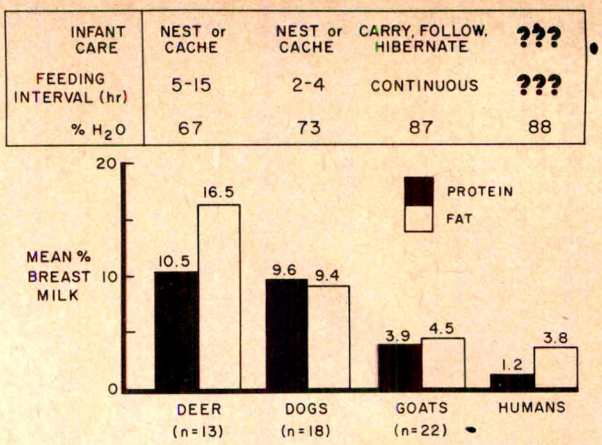

Fig 2.—Fat and protein content of mammalian milks and relationship to feeding intervals. Was human milk designed for infant who was continuous feeder? (Courtesy of Betsy Lozoff; from Klaus and Fararoff[20]).

have extended to this day and this hour, and have stimulated me to consider this question: Who shows the way and who follows? How we answer this question will certainly help us describe this modern revolution.

BREAST-FEEDING

During the 1970s, I have had the good fortune to go to a developing nation on many occasions. What I have seen has raised many questions that I would like to share with you.

First, who leads the way and who follows in regard to breast-feeding? The adults and children in the Mayan Indian village of Santa María Cauqué in the Guatemalan highlands were studied meticulously by Leonardo Mata and Juan Urrutia for a decade and a half.[4] The vast majority of mothers would be considered malnourished by our standards, but almost every mother in that village was able to breast-feed successfully for a mean period of two years. The clinically healthy mothers had at least three or four parasites or bacterial pathogens in their stools, some were ill with conditions that we would consider contraindications for breast-feeding, such as mastitis, acute respiratory infections, or shigella or salmonella enteritis. Even under these conditions, mothers do not stop breast-feeding. These women had no watches or clocks to time the intervals between feedings and put no soap or ointments on their nipples. They fed the baby when the baby wanted to suckle and as often and as long as the baby wished. They slept with their infant so nursing continued every few minutes through the night. It is this frequent nursing that appears to assure an abundant milk supply and provides maximum contraceptive effect. It is well-known that breast-fed babies have only one fourth to one fifth of the intestinal and respiratory infections of bottle-fed babies.[5] In a recent study, the average rural mother produced greater quantities of milk than the average poor or even well-to-do mother in the city. I wonder if these Mayan Indian mothers, whose practices have probably changed little over the last 1,000 years, do not have much to teach us about assisting nursing mothers and infants in the United States; for example, about the frequency of feeding an infant.

Fig 3.—Newborn baby, mother, and grandmother inside Indian home in village of Santa María Cauqué in Guatemalan Highlands (from Klaus and Kennell[21]).

The babies of our human ancestors were probably carried and nursed frequently for over 99% of our species' existence (Fig 1). For more than a million years, they lived as hunters and gatherers (from recently discovered foot prints, Mary Leakey says 3.6 million years [*National Geographic* 155:446-457, 1979]). They had the same skull, the same bone structure, and

perhaps some of the same behavior patterns as humans today. The small square in the lower right-hand corner of Fig 1 indicates the approximately 10,000-year period since the agricultural mode began, and the 200-year span of our present industrialized society is represented by an almost invisible dot, a period too short for evolutionary adjustments to occur. Other evidence suggesting that human mothers and infants may do best with frequent feedings is found in Ben Shaul's study of more than 100 mammalian milks[6] (Fig 2). Note the high fat and protein content of the mammals who feed their young at intervals of five to 15 or two to four hours (for example, deer and dogs), the decidedly lower fat and protein content of those who feed almost continuously (such as goats and nonhuman primates), and the still lower levels in the human. Was the human infant meant to breast-feed continuously?

Second, let's look at a series of observations in Guatemala in regard to the remarkable immunologic properties of breast milk. Figure 3 is a photograph of the inside of a Guatemalan home in the village of Santa María Cauqué with a newborn infant, her mother, and grandmother. Four days after this visit, a well-nourished American pediatrician who visited the home was laid low by crampy abdominal pains and watery diarrhea. On recovery, the pediatrician returned to the home and saw that the baby had remained completely healthy, as is true of most of the newborns in that village for the first three months of life. Neonatal mortality in this village is high (37 per 1,000 live births), mainly because of the high proportion of infants of less than 2,000 g birth weight. However, a birth weight of 2,750 g reliably predicted survival for the first three months.[4] In 15 years, there has been almost no morbidity in the first 28 days in infants born in the village, compared to many serious problems due to infection in infants born in the hospital. This can now be explained by several mechanisms. As you are probably aware, when a mother has an infection, such as pathogenic *Escherichia coli* enteritis, sensitized

Fig 4.—Mother carrying her infant on her back as she goes about her daily activities of tending sheep and llama, and spinning wool in Andes near Cuzco, Peru.

cells in her gastrointestinal (GI) tract migrate to the mammary glands to produce specific protection from the time of birth on. This protection is provided by secretory IgA antibodies in the mother's milk, which are not destroyed by proteolytic enzymes in the GI tract. Thus, we may be able to look to rural areas of developing countries for information about the process of breast-feeding and for evidence of its beneficial effects.

THE ROLE OF BODY CONTACT

Most travelers are amazed to note that they almost never hear a baby cry when they visit a developing country. It is particularly impressive to a US pediatrician who cannot remember a day when he did not have a phone call from a mother concerned about her crying baby. This leads to a third series of observations and questions about infant care. Was the human infant meant to cry except when in pain? Is crying due to a need for warmth, contact, and stimulation? The lack of infant crying in developing nations is often attributed to malnutrition, but many well-nourished, healthy, active, and responsive infants in these countries do not cry. As shown in the photograph of a mother from Cuzco in the Andes Mountains of Peru (Fig 4), the practice of our ancestors, the hunters and gatherers, for hundreds of thousands of years of carrying the baby on the mother's body and sleeping with the baby at night is still carried out in developing countries, which have a settled agricultural existence. The woman in Peru shows it is possible in some cultures for the mother to provide stimulation and breast-feeding for her infant while she is working. She is tending a flock of sheep and llama at the same time that she spins wool and provides the infant with stimulation and close contact. In most children's hospitals in the United States, about 1% to 3% of the admissions are for infants suffering from nonorganic failure-to-thrive, who often respond dramatically to human contact and stimulation. Does this practice of carrying the baby on the mother's body have relevance for us in the United States for failure-to-thrive? Does it have relevance for us in the United States for colic? For sleep problems? For separation problems? Who leads the way and who follows?

A fourth observation relates to tactile sensitivity to the infant's needs. Sierra Leone is one of many countries where every young mother is expected to be able to carry her baby on her body all day and detect the small changes in breathing and body movements that precede urination and defecation, so by one week she is able to care for her baby with no soiling of her clothes. She is considered a poor mother if she makes any misjudgment. For Eskimo mothers, a miscalculation could be disastrous because of wind-chill factors that result in freezing of the skin with exposures of less than 30 s. Mothers and fathers in the United States seldom learn how to pick up tactile signals from their babies and to achieve this state of fine-tuned responsiveness to the baby's needs. Christine Cooper reported in conversation (January 1978) that when mothers in Sierra Leone come to the clinic saying their infant has a urinary tract infection, they are almost invariably correct. How do they know? The baby would urinate frequently, and the usual signals were changed so the mothers's clothing would be soiled.

I am describing these patterns of behavior in other cultures to demonstrate principles, not to recommend their application in the United States without careful study. In no way do I

recommend skin-to-skin contact for the diagnosis of urinary tract infections, nor do I believe that mothers in the United States are ready to use the fine-tuned responsiveness to an infant without diapers in a carpeted home. However, we may get valuable hints and insights from observing different patterns of care in the context of evolutionary development. And then these can be studied scientifically. In Guatemala, for example, it may be possible to sort out elements that are related to the Indian's life-style of poverty, poor nutrition, and limited education, and to distinguish these from other components, such as success with breast-feeding, the children's joy in family and community life, and the ability of the adults to organize the community and rebound from catastrophies, such as the devastating earthquake in 1976 that destroyed all the adobe homes, killed 78, and injured 357 among 1,500 people in one village.[4]

CHILDBIRTH

Back in the United States, there is another set of statistics that reflects a growing concern of all of us. One million 15- to 19-year-old women become pregnant each year, or one tenth of all women in this age group. Thirty thousand girls younger than 15 years become pregnant and 13,000 give birth each year. The following observations concern preparation for motherhood and support for the pregnant teenager.

In the United States, the limits of adaptability of the teenage mother may be exceeded by the medicalization of childbirth, the provision of multiple clinics, and a shifting assortment of physicians and nurses during her pregnancy and delivery. Let us compare this with what happens in the village of Santa María Cauqué. Every child will be involved with the care of younger children, and every girl, through daily practice and on-the-job training, becomes expert by 12 years of age in the activities of a woman and mother in that culture: cooking, laundering, and child care. Childbirth in nonindustrialized societies is regarded as an integral part of ordinary family life. When the new mother in Fig 4 was 15 years of age, she had been going with a boy for about a year. When it was clear to her boyfriend's parents that a strong interest was developing, she was invited to help her future mother-in-law for several months to become accustomed to the family and their ways. Then, after a fiesta, the boy's parents asked him to bring the girl to live with them and share his bed from then on. Due to malnutrition, the onset of menstruation and ovulation is late, with the average age of menarche at 14½ years. Usually the first baby is born one year after marriage. By the time this girl was invited to live in her boyfriend's home, she was thoroughly familiar with all the activities of a woman and mother in that society. With the first sign of pregnancy, the boy's mother called in the native midwife. In Santa María Cauqué, no change in diet or activities is recommended. However, in other cultures the young mother-to-be is expected to adhere to a whole series of prescribed and proscribed activities with which everyone in the village agrees completely because they have been standard for centuries. Usually there are certain dietary restrictions. In some communities, there are recommendations of increased physical activity, in others reduced. In some villages, sexual intercourse is strongly encouraged through pregnancy, as it will lead to a stronger baby; and in others it is prohibited for the same reason. For many of the aches and pains associated with the pregnancy, the native midwife or the native healer has ready answers. In Santa María Cauqué, the woman works almost to the time of delivery.[4] Labor is short for primiparous deliveries, with a mode of four hours in 429 deliveries, a shorter time than stated in most textbooks. Few had a labor of more than eight hours. Almost all deliveries are in the kneeling position on a dirt floor or mat in the home, surrounded by supporting family members. There has been a remarkably low incidence of breech deliveries, 0.7% in contrast to the 2% or more quoted in most textbooks.[4] Does this give us ideas about what we should study in birth centers? There is no doubt that modern obstetrics has made remarkable advances and we do not want to lose the gains that have been made, but it is interesting to note that no preeclampsia or eclampsia were observed in any patient in Santa María during the 15 years of study. *No* cases of puerperal fever and *no* deaths of the mother during childbirth or puerperium occurred. Who shows the way and who follows?

SUPPORTIVE PERSON DURING LABOR AND DELIVERY

In an age of electronic monitoring of the fetus during labor, is there anything that we can learn by observing the effect of support during childbirth? This question leads to another set of observations. Consistency of care during pregnancy, labor and delivery, and the postpartum period is an important tradition in the villages and rural areas of many developing nations. In all but one of 38 cultures that have been studied by anthropologists, there is a woman who remains with a mother during labor and assists at birth. In Santa María Cauqué, the native midwife, both grandmothers, the husband, and occasionally the father-in-law are present. It is interesting that no children are allowed, as is true in most cultures, but they know what is happening. In 98% of all cultures, there is a tradition of postpartum confinement of the mother and baby together, and more than 50% of all societies will not allow a male doctor to be present at delivery. Ann Oakley[7] says that "the transition from control by laywomen to control by professionally trained men is the most crucial change that has occurred in the management of childbirth in industrialized society over the last 100 years."[7]

Let's look at a study in a busy obstetric hospital with a delivery system that was established by doctors and nurses from the United States. In a recent, carefully controlled study in Guatemala City, women who labored alone, which was the usual routine, were compared with women, randomly selected, who had an untrained woman present with them throughout labor. The presence of a supportive woman in a hospital setting signifi-

cantly reduced the length of labor from 19 to nine hours, strikingly decreased the incidence of obstetric and pediatric complications, such as meconium staining and fetal distress, and strongly influenced the behavior of the mother and her infant after delivery.[8]

You might be interested to know that in two maternity hospitals where separation of mother and baby was routine for the first 12 to 24 hours after delivery, all the mothers in these hospitals are now given their babies to keep and care for throughout the hospital course within one to two hours after delivery. This has resulted in the elimination of the central nursery and the provision of space for medical student and nursing student study and teaching sessions.

Fig 5.—Mothers feeding and caring for their own premature infants in Baragwaneth, South Africa. (Courtesy of Eric Kahn and Sam Wayburne from Klaus and Kennell[21]).

FAMILY PARTICIPATION IN HOSPITAL CARE

Another series of observations relate to family participation in the care of sick people. When we first traveled around Guatemala, we were told by a driver that the Indians were not very smart. There was a new hospital with the latest in medical, surgical, and operating room equipment. This hospital had restrictions on visiting times and on the number of visitors. The driver commented that the "dumb Indians" did not come to that hospital, but continued to go to the old adobe hospital in that region. The building was too small for the large number of patients who came for care, so they extended out into the surrounding area in uncovered and unprotected ward-like groupings. In this hospital, families lived-in with patients to provide for their care and to cook for them. Apparently this was important enough to the families that they were willing to give up the advantage of a more modern hospital.

Family participation also includes involving parents in the care of premature infants. In 1954 in Baragwaneth Hospital, South Africa, Eric Kahn and Sam Wayburne described their experiences with mothers living-in in the hospital and breast-feeding their infants (Fig 5). They showed a significant increase in the survival of the infants, with statistics comparable to the best university centers: and at a reduced cost.[9] In Ethiopia, Nebiat Tafari showed that by asking parents of premature babies to live-in the hospital and care for and breast-feed their infants in the premature nursery, he was able to care for three times as many infants, the mortality in the nursery decreased dramatically, and the number of surviving infants increased 500%. With care by parents, the cost of the care of an infant in his unit decreased from $120 in 1970 to $40 in 1972.[10,11] Who leads the way and who follows?

MEDICAL RECORDS

No talk by an old ambulatory pediatrician could avoid some mention of medical records. Is it possible that there are even some insights about records to be gained from developing countries? In his book, *Pediatric Priorities in the Developing World*, David Morley[12] describes the home-based record and emphasizes that the child's medical records are best entrusted to his mother from the time of birth or from the first visit onwards. From his long experience with an "under 5 clinic" and an "at risk clinic," he reports that the child's record is available at the time of a contact at home, in the clinic, or in the hospital in well over 95% of the visits and that there the loss of medical records is only about 1% per year, compared with losses of 5% to 10% in US clinic filing systems. When the mother brings the record, patients can be seen immediately. Should we follow, or at least study this alternative method of keeping records?

Here I would like to point out a new untapped source of research information and concepts about children. The Society for Research in Child Development (SRCD), which met in March 1979 in San Francisco and considered a wide range of fascinating topics. One was a study on "Sex Hormones in Umbilical Cord Blood: Their Relationship to Behavior at 4 Years," which showed a correlation between levels of testosterone and estrogens and rough-and-tumble play at age 4 years. (It was not the activity, but whether the child was the attacker or the one attacked that was related to the hormone level.) There were research reports on "Children's Understanding of Illness." "Peers as Therapeutic Agents," "Helping by 2-Year-Old Children," "Separation Distress Over the Life Span," "Pros and Cons of Infant Day Care," and "A Prospective Study of Nonorganic Failure-to-Thrive." An increasing number of pediatricians from the United States and around the world have found these meetings exciting and valuable. The studies of children by investiga-

tors from disciplines such as sociology, anthropology, and ethology may turn out to be as fundamental for ambulatory pediatricians as the traditional basic sciences have been for other pediatric subspecialists. The members of the SRCD may show us a new way.

PEDIATRICS LEADS THE WAY

At this point I will make a major shift and now consider where pediatrics has led the way and others have followed.

First, let's consider what pediatrics has contributed to adult medicine. Of course, pediatrics did arise in part from adult medicine and has been influenced by its practices and teachings, but what have we in pediatrics offered or what can we offer to our colleagues in adult medicine? The basic principles of fluid and electrolyte therapy were discovered and applied by pediatricians. The investigations of Gamble, Darrow, Wallace, and others resulted in the saving of thousands of infant lives throughout the world, but also made possible major improvements in the care of adults: for example, the successful treatment of cholera. The extremely important commitment of pediatricians to preventive medicine has brought an array of immunizations to adult medicine, as well as many other concepts of prevention.

The complex features of growth and development that appeared for several decades to be peculiar and limited to the pediatric age range have gradually influenced adult investigation and care in the biochemical, immunologic, and psychologic areas, with an increasing appreciation of changing fluid and electrolyte needs, the changing susceptibility to infection, and the significance of developmental stages, periods of crisis, and life-span studies, as emphasized in *Seasons of a Man's Life* by Daniel Levinson[13] and *Adaptation to Life* by George Vaillant.[14]

The benefits of a neutral thermal environment for low birth weight infants shown by pediatricians, starting with the studies of Silverman et al,[15] the concepts of temperature control they developed were picked up by those caring for adults and applied eight to ten years later to burn patients, and then later on to older cardiac patients, with improvements in outcome.

Fig 6.—Portrait of Ralph Izard, aged 12 years, by Jeremiah Theus, 1753. (High Museum of Art, Atlanta, Ga; anonymous donor.)

THE FUTURE AND THE PAST

What about the future? Who shows the way and who follows? Has pediatrics developed other aspects of care that can be of benefit for adult patients? I believe the answer is an emphatic "Yes." Let's consider a few possibilities.

Starting in a small way in a few hospitals, Child Life or recreational or play programs have made such a great improvement in the lives of hospitalized children. These programs provide an opportunity to play and express fears and anger, and prepare the child for operations, anesthesia, and procedures; there has been an explosion of these programs for hospitalized children and for children coming to ambulatory clinics.

Let me take a slight detour for a minute. If you have enjoyed the paintings by hospitalized or sick children, or if you find, as I do, that it is valuable to look at the past to get a view of the future, then I recommend wholeheartedly that you visit the Junior Gallery at the Atlanta High Museum of Art. There you will find an exhibit called "Children in America," which illustrates the changing images of childhood from colonial days to the present. The paintings span the years, from the time George Armstrong opened his clinic 210 years ago to the present. If you go, you will see paintings such as the one entitled "Ralph Izard" (Fig 6), painted in 1753.

Eighteenth-century artists painted sober, stiff youngsters, dour in face, erect in posture, adult in demeanor. Life was severe: one half of all youngsters died before the age of ten. Children were hurried into adult responsibilities. Here Ralph, 12 years old, is painted as lord of the manor that he inherited at age 7 years, stiffly gesturing toward his property. Another picture, "Wilson Children," painted around 1860, shows boys and girls dressed alike. Parents had begun to regard play as a natural, even educational, activity, so toys began to appear on artists' canvases, and children were shown in more informal poses. Another picture is called "Shoe Shine Boy," and shows the romanticized view of working children in the late 19th century, the up-from-nothing, sentimental, Horatio Alger success story. The exhibit also has pictures of the grim life of young children laboring in a mill or factory.

Please think for a minute about your image of the pediatric and the adult divisions of your hospital. Like the paintings of the children, I believe these divisions reflect social history or society's view of the care of children and adults. If you or adult members of your family have been hospitalized recently and benefited from modern surgical and technological advances, you may be aware of the need for an "Adult Life Program" in hospitals, similar to Child Life Programs. Over and over, we are impressed that our nursing and pediatric colleagues do not understand their own disease or treatment when they are hospitalized, or are afraid to ask. Adults have vivid fantasies, just as children do. Adult life workers and an adult life program could be of great value in these units, but shouldn't they be provided for all adult patients, even those who may

only be going through elective studies, who need preparation, information, and support? Shouldn't one person be provided to support each adult whose family or friends do not do this?

Members of the Ambulatory Pediatric Association have been leaders in the introduction and support of Child Life Programs. They have also pioneered in the development of programs for parents to live in the hospital with their young children. In turn, these have usually led to the establishment of parent discussion groups and more involvement of the entire family in visiting the hospital and caring for the sick youngster. Sir James Spence at Newcastle-upon-Tyne and James Robertson and Dermod McCarthy in Amersham, England, were innovators with these concepts and showed that children could be hospitalized with a minimum of disturbance if their parents lived in with them, in contrast to the child who was hospitalized alone.[16,17] The Care by Parent unit started by Vernon James[18] and further adapted by Morris Green stimulated the introduction of a large number of similar programs.

Does this have application to adults? I think it does. In reaction to the technological and impersonal aspects of institutional care and a torrent of requests from young, healthy couples, hospitals in almost every large city in the United States have opened homelike birth centers, where a woman in labor can have the father, friends, and any members of the family present during labor and delivery, can bring their favorite pictures and music, and can make some decisions about her care. These enthusiastic, energetic young adults have rocked the obstetric establishment through their insistence on a reconsideration of firmly held practices, such as the mother's position during labor and delivery, the routine use of episiotomy, and elective induction with pitocin. No hospital supply manufacturer in the United Kingdom or the United States has yet developed a double bed for hospital use, so it has been necessary for centers to innovate. The concept of allowing the father and mother to be together in bed with their newborn baby has set off an explosive reaction by many male doctors that somehow this is not right. (When fathers are allowed to live in with their wives, they do get into bed, and one cannot be certain about what goes on.) But seriously, a place for fathers in maternity divisions is important for many reasons.

Fig 7.—Future mothers in village of Santa María Cauqué.

Briefly, I would like to share the contents of a film of an interview of a couple who had a baby with Down's syndrome.[19] The mother describes vividly how important it has been for her husband to live in the hospital with her. In spite of the permission of the Chief of Pediatrics, the Chief of Obstetrics and the Chief of Nursing, the staff could not find a bed in this large hospital of 1,200 beds! It is not easy to bring in a new concept.

If those involved in adult medicine will follow the lead of ambulatory pediatricians and make it possible for adults to live in and provide care for family members, they will encounter some of the same problems of crowding and confusion that accompanied the introduction of unlimited visiting and parents living in with their children on the pediatric divisions. However, there is little doubt that there will be benefits for the adult patients as there are for young children. Just as families have taught us much about the care of children, so also, families will teach those in obstetrics and adult medicine and surgery much about the care of adults.

WHO LEADS AND WHO FOLLOWS?

There are many questions for us to consider. We view a pregnant woman in one fashion and the Indians and other preindustrial groups view her in another. Who leads whom? Should mothers sleep with their infants? Should mothers be encouraged to carry their babies on their bodies? Or is this impractical for women in our society? Should pregnant mothers be encouraged to keep active physically almost to the time of delivery? Is there a way to involve young women and men in child care in the home, or in school? Should we make a drastic change in hospital care and do as we do in ambulatory care, turn over full responsibility to the family for feeding and bathing the hospitalized child and giving oral medications?

Would the presence of a supportive woman with every mother laboring and delivering in the United States decrease the need for obstetric interventions and help prevent neonatal asphyxia? Should we entrust children's medical records to their parents?

What novelties are we suppressing? Are we at a major turning point in scientific development? What does it

mean that some of the methods of birthing and child care in developing countries do not fit in with what we consider the best modern style of living? I do not have the answer to these questions.

Before concluding, I want to make it clear that in this International Year of the Child I am not ignoring the great scientific advances in North America. I want to emphasize that I have described these patterns of behavior in other cultures so that we might look for principles, not to recommend their application in the United States. I do not want to suggest that we go back to what is going on in Santa María Cauqué (Fig 7), but we can get hints and ideas from preindustrial cultures that may open up vistas in our understanding. Modern medicine has made many significant advances, but a few of these may be steps backward. Our scientific revolution may hinge on choosing the most promising components from our evolutionary past and testing these against our modern practices, in long-term studies, with consideration of the broadest ramifications. Then we will determine who shows the way and who follows.

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References

1. Kuhn TS: *The Structure of Scientific Revolutions*. Chicago, University of Chicago Press, 1968.
2. Watson JB: *Psychological Care of Infant and Child*. New York, W W Norton & Co Inc, 1928.
3. Still GF: *The History of Paediatrics*. London, Oxford University Press, 1931.
4. Mata LJ: *The Children of Santa María Cauqué: A Prospective Field Study of Health and Growth*. Cambridge, Mass, MIT Press, 1978.
5. Sosa R, Kennell J, Klaus M, et al: The effect of early mother-infant contact on breastfeeding, infection and growth, in Elliott K, Fitzsimons DW (eds): *Ciba Foundation Symposium 45: Breastfeeding and the Mother*. Amsterdam, Elsevier Publishing Co, 1976, pp 179-193.
6. Ben Shaul DM: Notes on hand-rearing various species of mammals. *Int Zoo Year Book* 4:300-301, 1962.
7. Oakley A: Cross cultural practices, in Chard T, Richards M (eds): *Benefits and Hazards of the New Obstetrics*. Lavenham, England, Lavenham Press Ltd, 1977, pp 18-33.
8. Sosa R, Kennell J, Klaus M, Urrutia J: The effect of a supportive woman on mothering behavior and the duration and complications of labor, abstracted. *Pediatr Res* 13:338, 1979.
9. Kahn E, Wayburne S, Fouche M: The Baragwanath premature baby unit: An analysis of the case records of 1,000 consecutive admissions. *S Afr Med J* 28:453-456, 1954.
10. Tafari N, Ross SM: On the need for organized perinatal care. *Ethiop Med J* 11:93-100, 1973.
11. Tafari N, Sterky G: Early discharge of low birthweight infants in a developing country. *Environ Child Health* 20:73-76, 1974.
12. Morley D: *Paediatric Priorities in the Developing World*. London, Butterworth Inc, 1973.
13. Levinson DJ: *Seasons of a Man's Life*. New York, Alfred A Knopf Inc, 1978.
14. Vaillant GE: *Adaptation to Life*. Waltham, Mass, Little Brown & Co, 1977.
15. Silverman WA, Fertig JW, Berger AP: The influence of the thermal environment upon the survival of newly born premature infants. *Pediatrics* 22:876-886, 1958.
16. Spence J: *Thousand Families in Newcastle-upon-Tyne*. London, Oxford University Press, 1954.
17. Robertson J: *Young Children in Hospitals*. New York, Basic Books Inc Publishers, 1959.
18. James VL, Wheeler EW: The care-by-parent unit. *Pediatrics* 43:488-494, 1969.
19. Kennell J: *Discussions With Parents of a Malformed Baby*, videotape produced and distributed by Health Sciences Communication Center, Case Western Reserve University, Cleveland, 1976.
20. Klaus MH, Fararoff AA: *Care of the High Risk Neonate*. Philadelphia, WB Saunders Co, 1979.
21. Klaus MH, Kennell JH: *Maternal-Infant Bonding*. St Louis, CV Mosby Co, 1976.

Radiological Case of the Month

Lionel W. Young, MD;
Contributed by Herman Haimovici, MD; Richard J. LaVigne, MD; Terry T. Howard, MD

From the Departments of Radiology (Drs Haimovici and LaVigne) and Obstetrics and Gynecology (Dr Howard), Medical Associates, Chelmsford, Mass.

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A 34-year-old woman was sent for ultrasound examination "because [of] a disproportionally large uterus for the dates." Physical examination and previous medical history were unremarkable. Her obstetrical history was two normal pregnancies from a first marriage and from a second marriage, a spontaneous abortion and a stillborn baby at 25 weeks with harelip, cleft palate, and low-set ears. The ultrasound examination (Fig 1) shows a fetus of approximately 28 weeks' gestation, with a large mass around the head and the neck. Three weeks after the ultrasound examination, fetal death occurred and a cesarean section was performed.

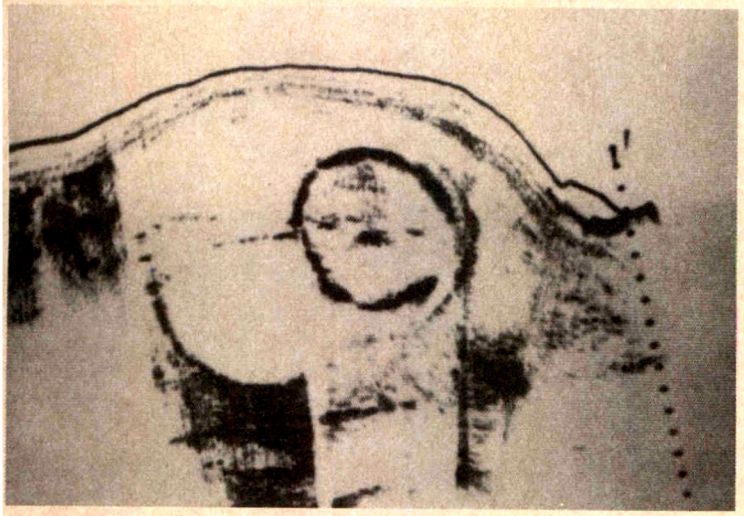

Figure 1.

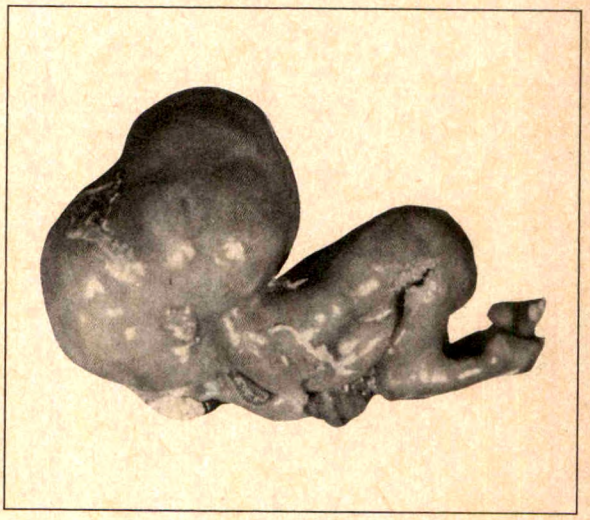

Figure 2.

Denouement and Discussion

Fig 1.—Longitudinal scan 2 cm to left of midline.

Fig 2.—Fetus with large hygroma involving neck and posterior aspect of head.

Hygroma (Cystic Lymphangioma): Diagnosis by Ultrasound

Hygroma's are congenitally modified lymphatics presenting as a large single cavity or as multilocular fluid cavities. Most often they develop on one side of the neck, but may be found in other locations. The cysts, filled with clear straw-colored fluid, are lined by a single layer of flat endothelial cells and surrounded by connective tissue and smooth muscles. They are not compressible and not visibly connected with lymphatic channels. They may increase in size after birth because of the increased secretion of fluid. Abortion, as in this case however, is not a rare occurrence. Evacuation of fluid gives only temporary relief and unless the endothelial wall is completely destroyed the fluid will reappear. As the cyst enlarges, rupture and bleeding followed by calcification and fibrosis may occur.

With the gray scale and real-time modes of ultrasound, prenatal diagnosis of cystic hygroma after 14 weeks of pregnancy is possible, as demonstrated in our case. A large echo-free and septate structure is very suggestive of a hygroma.

Differential diagnosis should include failure of proper closure of the neural tube with resultant spina bifida and meningocele. Strict posterior location of the cystic mass and an associated increase of α-fetal protein in the blood and amniotic fluid are hallmarks of this diagnosis. A branchial cleft cyst due to the failure of closure of the embryonic branchial cleft appears also as an echo-free area over the lateral side of the neck, but is usually much smaller in size. From an obstetrical point of view, prenatal diagnosis of a large hygroma is important because it requires cesarean section.

Donald Agostinelli, MD, provided the photograph of the fetus.

References

1. Lee TG, Newton BW: Posterior fossa cyst prenatal diagnosis by ultrasound. *J Clin Ultrasound* 4: 1976.

2. Morgan CL, Haney A, Christakos A, et al: Antenatal detection of fetal structural defects with ultrasound. *J Clinic Ultrasound* 3:287-290, 1975.

3. Shaub M, Wilson R, Collea J: Fetal cystic lymphangioma: Prepartum ultrasonic findings. *Radiology* 121:449-450, 1974.

4. Potter EL: *Pathology of the Fetus and the Newborn*. Chicago, Yearbook Medical Publishers, 1953, chap 12.

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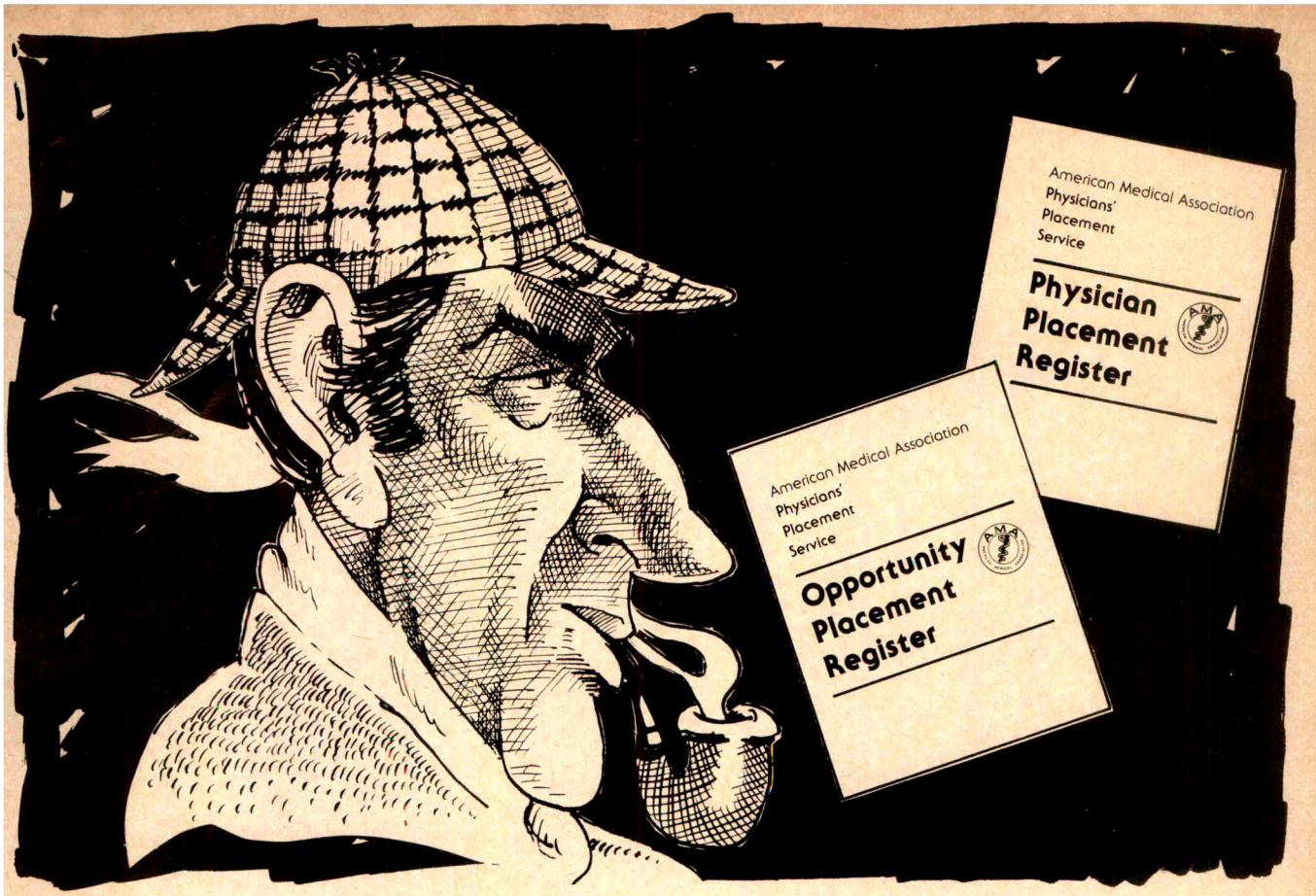

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Each teaspoonful (5 ml.) of syrup contains:

Phenylpropanolamine hydrochloride	20.0 mg.
Phenylephrine hydrochloride	5.0 mg.
Phenyltoloxamine citrate	7.5 mg.
Chlorpheniramine maleate	2.5 mg.

Each pediatric formulation contains the following ingredients:	Pediatric Syrup each 5 ml. contains:	Pediatric Drops each 1-ml. dropper contains:
Phenylpropanolamine hydrochloride	5.0 mg.	5.0 mg.
Phenylephrine hydrochloride	1.25 mg.	1.25 mg.
Phenyltoloxamine citrate	2.0 mg.	2.0 mg.
Chlorpheniramine maleate	0.5 mg.	0.5 mg.

ACTIONS: Naldecon is useful for the relief of nasal congestion associated with pollen allergy and minor infections of the upper respiratory tract (the common cold, nasopharyngitis, acute and chronic sinusitis). Naldecon tablets are compounded with half of each ingredient in the outer layer for immediate action and the remainder in the slowly disintegrating core for a sustained effect.

The actions and uses of individual ingredients in the formulation are as follows:

Phenylpropanolamine Hydrochloride

Phenylpropanolamine hydrochloride[1] acts similarly to ephedrine. It is effective orally for the symptomatic control of allergic manifestations, such as perennial hay fever and bronchial asthma. Its action is more prolonged than that of ephedrine, and it is not so apt to produce anxiety complex as is ephedrine.

Phenylephrine Hydrochloride

Phenylephrine hydrochloride[2] is a more powerful vasoconstrictor than synephrine tartrate. When administered orally, it is a vasopressor and relatively nontoxic. The pressor and anti-allergic effects of the drug are produced by oral administration. Therefore, this route may be employed in the treatment of orthostatic hypotension and allergic disorders. The comparatively larger doses required for effective oral treatment are only rarely accompanied by mild gastrointestinal symptoms. These may be avoided by administering the drug after meals.

Phenyltoloxamine Citrate

Phenyltoloxamine citrate[3] is a β-dimethylaminoethyl ether of orthobenzylphenol; as such it belongs to the group of antihistaminics exhibiting the aminoalkyl ether structure. The incidence of side effects is low; at recommended doses, soporific effects occur in less than 7% of patients.

Chlorpheniramine Maleate

Chlorpheniramine maleate[4] has good therapeutic efficacy and low incidence of side effects. It is comparable in therapeutic efficacy to other antihistaminics although administered in very low dosage.

INDICATIONS: Relief of distressing symptoms of colds and other upper respiratory infections, acute and chronic sinusitis, hay fever and other pollen allergies:

Rhinorrhea	Lacrimation
Postnasal drip	Sneezing
Nasal congestion	Itching of eyes and nose
Sinus congestion	Head stuffiness

CONTRAINDICATIONS: Sensitivity to any of the ingredients.

PRECAUTIONS: This preparation may cause drowsiness. The patient should be cautioned against engaging in operations requiring alertness such as driving an automobile, operating machinery, etc. Do not exceed the recommended dose unless directed by a physician. Individuals with high blood pressure, heart disease, diabetes mellitus, thyroid disease, glaucoma, peripheral vascular disease or prostatic hypertrophy should use only as directed by a physician.

DOSAGE: This chart represents single dosages for the products listed below. Usual dosage schedule for Naldecon Pediatric Drops, Naldecon Pediatric Syrup and Naldecon Syrup is every 3 to 4 hours, not to exceed four doses in a 24-hour period. For sustained-action Naldecon Tablets, doses should be administered on arising, in midafternoon and at bedtime.

Single Dosage for...	Pediatric Drops	Pediatric Syrup	Syrup	Tablets
3 to 6 months	1/4 ml.			
6 to 12 months	1/2 ml.	1/2 teaspoonful		
1 to 6 years	1 ml.	1 teaspoonful		
6 to 12 years		2 teaspoonfuls	1/2 teaspoonful	1/2 tablet
over 12 years			1 teaspoonful	1 tablet

REFERENCES:

1. New and Nonofficial Remedies 1955.
2. New and Nonofficial Remedies 1954.
3. A.M.A. Council on Drugs Monograph on Phenyltoloxamine, J.A.M.A. 163:357 (2/2/57).
4. New and Nonofficial Drugs 1959.

SUPPLY:

NDC 0015-5600—Naldecon Tablets
NDC 0015-5601—Naldecon Syrup
NDC 0015-5615—Naldecon Pediatric Drops
NDC 0015-5616—Naldecon Pediatric Syrup

For information on package sizes available, refer to the current price schedule.

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Isolated Growth Hormone Deficiency and Cystic Fibrosis: A Report of Two Cases

Cystic fibrosis (CF), an inherited, chronic progressive disease, is considered a cause of failure to thrive and retarded growth. In fact, special growth curves have been constructed for patients with CF.[1,2] However, most patients with CF who survive to adulthood achieve stature in the normal range.[3] Thus, when severe growth retardation is observed in a patient with CF, it should not be attributed to CF alone and other etiologies should be sought. We have described two patients with CF who have isolated human growth hormone (HGH) deficiency.

Report of Cases.—CASE 1.—A 14-year, 8-month-old boy was found to have elevated sweat sodium and chloride concentrations at age 2 years, 9 months during an evaluation for short stature. However, at that time, he had no demonstrable respiratory or gastrointestinal disease, and other than his size and a submucosal cleft palate, physical examination showed no abnormalities. By age 5 years, however, he had had occasional symptomatic pulmonary infection and chronic changes on chest roentgenogram, and a diagnosis of CF was made. He had normal fecal fat excretion and normal pattern of amylase isozymes; and though duodenal intubation could not be accomplished, he seemed to have normal exocrine pancreatic function. His chest roentgenogram now shows coarsened peribronchial markings, early bronchiectatic changes, and hyperinflation. Sputum cultures contain *Pseudomonas aeruginosa*. At age 6 years, 9 months, deficiency of HGH was reported. Evaluations of serum calcium and phosphorus levels and liver, renal, and thyroid function have been normal. Evaluation of the pituitary-adrenal axis included normal AM and PM plasma cortisol, urinary 17-hydroxycorticosteroid and 17-ketosteroid values, and normal responses to corticotropin infusion and metyrapone tests. Within the last six months, normal pubertal changes have been observed. Pertinent data are summarized in the Table. Treatment with human growth hormone for eight years has restored normal growth velocity, and his height has paralleled the first percentile height curve.

Relevant family history includes an older brother, aged 15 years, who has CF (sweat chloride concentration, 125 mEq/L, mean of six determinations; range, 101 to 142 mEq/L). He has normal exocrine pancreatic function documented by determination of trypsin and chymotrypsin activity in his duodenal aspirate and a normal amylase isozyme pattern. Peribronchial thickening is present on chest roentgenogram and a heavy growth of *Staphylococcus aureus* is routinely found in his sputum. However, he has grown normally with a height in the 45th percentile and a weight in the 85th percentile.

CASE 2.—A 7-year, 5-month-old girl was found to have CF at four months of age and was begun on a regimen of pancreatic enzyme replacement at that time. Pancreatic insufficiency was documented by the absence of amylase, lipase, trypsin, and chymotrypsin activity in a duodenal aspirate. Her pulmonary status has been good, however; and chest roentgenogram has remained normal though sputum cultures contain *S aureus* and *P aeruginosa*. At age 4 years, 11 months, she was evaluated for short stature and found to have HGH deficiency. Serum calcium and phosphorous levels and liver, thyroid, and renal functions were normal. Assessment of the pituitary-adrenal axis included AM and PM plasma cortisol and urinary 17-hydroxycorticosteroid and 17-ketosteroid tests, the results of which were normal. Pertinent data are summarized in the Table. Human growth hormone replacement therapy was started, and she has shown an appropriate response. Three siblings, none of whom has CF, are all of normal stature.

Comment.—Although the conditions of these two patients have been well documented to be CF, a chronic disease capable of causing growth retardation, the degree of growth failure was out of proportion to the minimal degree of involvement of CF-related illness, and their heights and weights were more than 2 SDs below the mean even for patients with CF. Patient 1 has normal pancreatic function, so his growth failure cannot be explained by malabsorption. Patient 2 has pancreatic insufficiency, but she has been receiving treatment since the age of 4 months. Moreover, Sproul and Huang[1] found no correlation between pancreatic insufficiency and the degree of growth retardation in their series of patients with CF. Both patient 1 and patient 2 had normal chest roentgenograms at the time growth failure was noted, so chronic pulmonary disease cannot explain their short stature. Besides, the data of Sproul and Huang[1] indicated that severe pulmonary disease exerts its greatest influence during the adolescent growth spurt, not during early childhood when these patients were identified.

The diagnosis of HGH deficiency is also well established in our two patients. This finding probably represents a chance coexistence in these individuals. It is unlikely that the decreased plasma HGH level is secondary to some aspect of CF since both resting and stimulated plasma levels of HGH in patients with CF have been reported to be normal.[4,5] In addition there was no history of trauma or illness that could cause HGH deficiency secondarily.

Other causes of short stature that have been reported in association with CF include Down's, cri-du-chat, and Silver-Russell syndromes.[6] Of these syndromes, Silver-Russell dwarfism is the most difficult to exclude; however, plasma HGH levels have been documented to be normal in this group of patients.[6] In addition, our patients did not have the typical physical findings of these syndromes, and results of chromosomal studies were normal.

It is important for several reasons to diagnose HGH deficiency in patients with CF when it is present. Patients with CF, now living longer than ever before,[7] have many concerns about their physical habitus,[8] and correction of as many abnormalities as possible is desirable for optimal psychological adjustment. These children frequently have barrel chest, chronic cough, and greatly reduced weight for height even with optimal care; and amelioration of extremely short stature may well improve their self-image and their social function.

Also, correction or partial correction of a deficiency in the HGH level may

Clinical Data*	Case 1, M		Case 2, F	
	Time of Diagnosis	Present†	Time of Diagnosis	Present‡
Age, yr, mo	6, 9	14, 8	4, 11	7, 5
Height, cm	103.5 (−3.5 SDs)	146.5 (−3 SDs)	82.0 (−6 SDs)	92.9 (−5.5 SDs)
Weight, kg	16.0 (−3 SDs)	37.5 (−2 SDs)	9.9 (−3.5 SDs)	11.7 (−3.5 SDs)
Bone age, yr, mo	2, 0	12, 6	1, 0	2, 6
Height age, yr, mo	3, 9	10, 8	1, 6	2, 6
Chest roentgenogram	Peribronchial thickening	...	Normal	Peribronchial thickening
Skull roentgenogram	Normal	Normal	Normal	Normal
Sweat analysis				
Cl, mEq/L§	120 (102-129)	...	118 (110-121)	...
K, mEq/L§	18 (16-19)	...	15 (14-16)	...
Na, mEq/L§	125 (120-136)	...	104 (97-109)	[redacted]
Stool				
Fat, g/24 hr	1.1	...	25.6‖	...
% of fat intake	1	...	30	...
Serum				
Growth hormone, ng/mL				
Resting	1	...	1	...
Maximal response to				
Levodopa, 500 mg/1.73², oral	3	...	3	...
Arginine hydrochloride, 500 mg/kg, IV	5	...	3	...
Insulin injection 0.1 unit/kg, IV	3	...	3	...
T_3, RIA, ng/mL [80-170]¶	115	...	126	...
T_4, RIA, μg/dL [4.7-11.1]	6.2	...	10.3	...
TSH, lμU/mL [0.0-10.0]	< 2	...	2.7	...
LH, lmU/mL [1-6]	5:6	...	3.2	...
FSH, lmU/mL [2-11]	3.1	...	3.5	...

*IV indicates intravenous; RIA, radioimmunoassay; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.
†Treatment with human growth hormone injections begun at age 6 years, 9 months.
‡Treatment with human growth hormone injections begun at age 5 years, 6 months.
§Mean and (range) for four determinations.
‖Supplemental pancreatic enzyme therapy discontinued during collection.
¶ Normal range indicated in brackets.

favorably influence the course of the pulmonary disease in CF. The lung continues to grow throughout childhood, and during the first 8 years, much of this growth is accomplished by an increase in number of mature and immature alveoli.[9] One might speculate that if this growth fails to occur, the chronic infection present in CF patients would destroy the existing lung tissue without compensation from new growth.

The importance of the influence of HGH on lung growth and function has been supported by clinical studies of patients with hypopituitarism[10] and patients with acromegaly.[10,11] Moreover, therapy with human growth hormone has been shown to increase muscle mass, and respiratory muscle endurance has been postulated as one factor that benefits the course of CF lung disease.[12] Additionally, treatment with human growth hormone has been shown to result in increased blood volume in HGH-deficient children,[13] which would be important for oxygen-carrying capability and might benefit tissue oxygenation in patients with CF. Thus, it would seem desirable from both physiologic and psychologic standpoints to locate patients with CF who have HGH deficiency and to treat them appropriately.

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Nonproprietary Names and Trademarks of Drugs

Arginine hydrochloride—*Argivene.*
Corticotropin—*Actest, Acthar, Cortrophin, Depo-ACTH, Duracton, Actrope.*
Levodopa—*Bendopa, Dopar, Larodopa.*

1. Sproul A, Huang N: Growth patterns in children with cystic fibrosis. *J Pediatr* 65:664-676, 1964.
2. Kreibl T, Bender SW, Mörchen R, et al: The physical development of children with cystic fibrosis. *Z Kinderheilkd* 113:93-110, 1972.
3. Di Sant'Agnese PA, Davis PB: Cystic fibrosis in adults: 75 cases and a review of 232 cases in the literature. *Am J Med* 66:121-132, 1979.
4. Handwerger S, Roth J, Gorden P, et al: Glucose intolerance in cystic fibrosis. *N Engl J Med* 281:451-461, 1969.
5. Biswas S, Norman AP, Baffoe G, et al: Prolactin, growth hormone and α-fetroprotein in children with cystic fibrosis. *Clin Chim Acta* 69:541-542, 1976.
6. Taussig LM, Braunstein GD, White BJ, et al: Silver-Russell dwarfism and cystic fibrosis in a twin: Endocrine, chromosomal, dermatoglyphic, and craniofacial studies. *Am J Dis Child* 125:495-503, 1973.
7. Warwick WJ, Pogue RE, Gerber HU, et al: Survival patterns in cystic fibrosis. *J Chronic Dis* 28:609-622, 1975.
8. Boyle IR, di Sant'Agnese PA, Sack S, et al: Emotional adjustment of adolescents and young

dults with cystic fibrosis. *J Pediatr* 88:318-326, 1976.
9. Polgar G: The influence of pulmonary growth and development on paediatric respiratory diseases. *Acta Paediatr Acad Sci Hung* 15:183-191, 1974.
10. Jain BP, Brody JS, Fisher AB: The small lung of hypopituitarism. *Am Rev Respir Dis* 108:49-55, 1973.
11. Toppell KL, Atkinson R, Whitcomb ME: Lung growth in acromegaly. *Am Rev Respir Dis* 108:1254-1258, 1973.
12. Keens TG, Krastins IRB, Wannamaker EM, et al: Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. *Am Rev Respir Dis* 116:853-860, 1977.
13. Linderkamp O, Butenandt O, Mader T, et al: The effect of growth hormone deficiency and of growth hormone substitution on blood volume and red cell parameters. *Pediatr Res* 11:885-889, 1977.

Hodgkin's Disease as Epitrochlear Adenopathy

The most common initial manifestations of Hodgkin's disease in children are cervical or supraclavicular adenopathy or a mediastinal mass. Axillary and inguinal lymph node involvement are much less frequent. Epitrochlear involvement is very unusual, even in the presence of generalized disease and is extremely rare as an initial and isolated manifestation of Hodgkin's disease.

Report of a Case.—A healthy 6-year-old girl, had a firm, painless, 4-cm, right epitrochlear mass. There was no history of the systemic symptoms (ie, fever, sweats, weight loss, or pruritus), local infection, animal bites or scratches, or medications. The physical examination was otherwise unremarkable.

An excisional biopsy specimen demonstrated nodular sclerosing Hodgkin's disease. Clinical assessment included complete blood cell count, sedimentation rate, liver function tests, chest tomography, gallium scan, liver-spleen scan, bipedal lymphangiography, intravenous pyelogram and bilateral posterior iliac crest bone marrow aspirates, and biopsy specimens, all of which showed no evidence of lymphoma. A staging laparotomy was not done.

The child was treated with a six-month course of multiagent chemotherapy (mechlorethamine hydrochloride, vincristine sulfate, vinblastine sulfate, procarbazine hydrochloride, and prednisone) without complication. She remains well with no evidence of recurrent disease 14 months since diagnosis.

Comment.—Epitrochlear nodal involvement in Hodgkin's disease is very unusual, even in the presence of generalized disease, but it is particularly rare as an initial manifestation. Among 300 patients treated at Yale University, New Haven, Conn, from 1958 to 1977, there were only two instances of epitrochlear involvement, both in patients with advanced disease.[1] Among 109 children with Hodgkin's disease at the Princess Margaret Hospital, Toronto, epitrochlear adenopathy was not seen.[2] Kaplan[3] noted only three instances of epitrochlear involvement among more than 300 consecutive patients of all ages. Firth[4] described a single adult with epitrochlear adenopathy as an initial and sole manifestation of Hodgkin's disease. More recently, an adult with widespread disease was described who had an epitrochlear mass.[5] In contrast to Hodgkin's disease, epitrochlear nodal involvement is more common in the non-Hodgkin's lymphomas, although still relatively infrequent.[6]

The patient described in this article received combination chemotherapy without radiation in an attempt to avoid cessation of radial and humeral epiphyseal bone growth associated with therapeutic doses of irradiation.[7,8] Whether chemotherapy alone for localized disease will have the same high cure rate as intensive radiotherapy remains to be firmly established.[9]

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Nonproprietary Names and Trademarks of Drugs

Vinblastine sulfate—*Velban.*
Vincristine sulfate—*Oncovin.*

References

1. Prosnitz LR, Montalvo RL: The therapy of Hodgkin's disease, 1978: A combined modality approach. *Prog Clin Cancer* 7:97-113, 1978.
2. Jenkin RDT, Brown TC, Peters MV, et al: Hodgkin's disease in children: A retrospective analysis: 1958-1973. *Cancer* 35:979-990, 1975.
3. Kaplan HS: *Hodgkin's Disease.* Cambridge, Mass, Harvard University Press, 1972, pp 196-197.
4. Firth LA: Hodgkin's disease presenting at the elbow. *Lancet* 2:111, 1978.
5. Sacks PV, Saab G: Hodgkin's disease presenting at the elbow. *Lancet* 2:476, 1978.
6. Fuks Z, Glatstein E, Kaplan HS: Patterns of presentation and relapse in the non-Hodgkin's lymphomata. *Br J Cancer* 31:286-297, 1975.
7. Probert JC, Parker BR, Kaplan HS: Growth retardation in children after megavoltage irradiation of the spine. *Cancer* 32:634-639, 1973.
8. Parker RG, Berry HC: Late effects of therapeutic irradiation on the skeleton and bone marrow. *Cancer* 37:1162-1171, 1976.
9. Olweny CLM, Katangole-Maidde E, Kiiro C, et al: Childhood Hodgkin's disease in Uganda: A ten-year experience. *Cancer* 42:787-792, 1978.

Seropositive Rheumatoid Arthritis in a Patient With Cystic Fibrosis

There have been sporadic reports in the literature of the coexistence of cystic fibrosis (CF) with various forms of arthritis.[1-5] We have recently observed a case of classical, seropositive, adult-type rheumatoid arthritis in a female teenager with CF.

Report of a Case.—A 16-year-old girl had her condition diagnosed as cystic fibrosis at age 3 months, with a history of steatorrhea, respiratory symptoms, and a positive sweat electrolyte test; a brother had died from the same disease. Her growth and development were higher than the 50th percentile, and she had only minor morbidity from pulmonary or gastrointestinal symptoms. Her condition was intermittently treated with prophylactic antibiotics and she received a maintenance dose of daily pancreatic extract. As rated by the Schwachman score, her clinical CF status was "excellent."

At age 14 years, she noted the insidious onset of pain and swelling in the proximal interphalangeal (PIP) joints of the right first and second fingers. She experienced similar pains and swelling that rapidly developed in additional PIP and metacarpophalangeal (MCP) joints of both hands. After six months, the joints involved included the wrists, elbows, knees, and feet; a symmetrical, progressive, additive, inflammatory polyarthritis had evolved. Associated constitutional symptoms of fatigue and morning stiffness (two hours) were also present.

Examination showed swelling and tenderness of the second, third, and fourth PIP and MCP joints bilaterally, plus tenderness of the wrists. A subcutaneous nodule was present over the left olecranon region. Severe clubbing of the fingertips was present, but this antedated the arthritis by many years and was distinguishable from the inflammatory joint disease.

Her hemoglobin level was 12.8 g/dL, the ESR (Westergren) was 33 mm/hr, and a persistently positive latex fixation test for rheumatoid factor at a titer of 1:1280 was found. Other routine blood studies were unremarkable. Urinalysis and roentgenograms of the affected joints were normal.

Initially, the patient was treated with various nonsteroidal antiinflammatory drugs, including high doses of aspirin, tolmetin sodium, etc. After several months of observation, the persistent symptoms, progressive nature of her arthritis, decreasing

hemoglobin level (to 9.1 g/dL), and increasing ESR led to start of chrysotherapy with gold sodium thiomalate. After the patient had received a total dose of 585 mg of gold in weekly divided doses of 50 mg, proteinuria was noted; this eventually reached a level of 10 g/24 hr. Gold therapy was discontinued, the proteinuria eventually resolved completely, and therapy was instituted with hydroxychloroquine sulfate, 200 mg twice daily. After four months of therapy with this medication, a substantial remission has ensued, characterized by disappearance of objective joint inflammation, subsidence of morning stiffness to less than 20 minutes, and an increase in hemoglobin level to 11.9 g/dL. The rheumatoid factor titer, ESR, and pulmonary disease were unchanged.

Comment.—Several causes of joint pain in patients with CF may be encountered. Hypertrophic pulmonary osteoarthropathy with joint pains and appropriate radiologic changes is a well-known finding in many cases of CF.[1] Newman and Ansell[2] recently reported a study of five patients with CF who had transient arthritis involving the large joints, which resolved spontaneously in one to ten days. These patients also had an erythematous rash contiguous with the affected joints, and they were all seronegative for rheumatoid factor. Our patient had a seropositive, progressive, sustained arthritis unassociated with any rash and does not fit this category.

Mathieu et al[3] reviewed several patients with "rheumatoid arthritis" and pulmonary infection. Five patients in their series had positive rheumatoid factor tests, but two of these had bronchiectasis (rather than CF) as their primary pulmonary problem. Of the three seropositive patients with CF, two had pauciarticular arthritis associated with low titers of rheumatoid factor, and neither patient would seem to meet currently accepted criteria for classification of rheumatoid arthritis. One of their patients, a 19-year-old woman, had a strongly positive rheumatoid factor test associated with pain, swelling, and stiffness of numerous joints, and this patient's condition would seem to have also been a case of seropositive rheumatoid arthritis with CF. The current case, however, seems to be the first to have had nodules in addition to the other classic manifestations of adult-type rheumatoid arthritis.

A few minor causes of joint pain in patients with CF have also been reported. A 6½-year-old patient had a seronegative polyarthritis followed two years later by the manifestations of Crohn's disease.[4] (In our CF clinic, we are currently following up a 26-year-old woman with biopsy specimen-proved Crohn's disease who has never had arthritis.) Some patients with CF have hyperuricemia that can be secondary to administration of large doses of supplemental pancreatic enzymes.[5] Patients with pancreatic disease are also subject to certain forms of arthritis.[6]

The development of a positive test for rheumatoid factor in chronic inflammatory states is well documented.[7] However, patients with CF, despite the fact that they have multiple pulmonary infections, do not have a higher incidence of rheumatoid factor than normal populations.[8] In the present case, the appearance of the rheumatoid factor in the serum was coincident with the development of the arthritis and was probably not a manifestation of chronic antigenic stimulation from an infectious source. It remains to be seen if the coexistence of the two disorders in this patient will enhance the risk of pulmonary infection in later years.

Since there is an enlarging population of patients of increasing longevity who have CF, many such patients can be expected to get the diseases of adulthood. We have reported a case of classical, seropositive rheumatoid arthritis of the adult type in a 16-year-old girl with CF. This may have been fortuitous, but it remains to be seen whether patients with CF may indeed have an increased incidence of this or other connective tissue disorders as they grow older.

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Nonproprietary Name and Trademark of Drug

Tolmetin sodium—*Tolectin.*

1. Matthay MA, Matthay RA, Mills DM, et al: Hypertrophic osteoarthropathy in adults with cystic fibrosis. *Thorax* 31:572-575, 1976.

2. Newman AJ, Ansell BM: Episodic arthritis in children with cystic fibrosis. *J Pediatr* 94:594-596, 1979.

3. Mathieu JP, Stack BHR, Dick WC, et al: Pulmonary infection and rheumatoid arthritis. *Br J Dis Chest* 72:57-61, 1978.

4. Euler AR, Ament ME: Crohn's disease: A cause of arthritis, oxalate stones, and fistulae in cystic fibrosis. *West J Med* 125:315-317, 1976.

5. Stapleton FB, Kennedy J, Nousia-Arvanitakis N, et al: Hyperuricemia due to high-dose pancreatic extract therapy in cystic fibrosis. *N Engl J Med* 295:246-248, 1976.

6. Tannenbaum H, Anderson LG, Schur P: Association of polyarthritis, subcutaneous nodules, and pancreatic disease. *J Rheumatol* 2:14-20, 1975.

7. Bartfeld H: Distribution of rheumatoid factor activity in non-rheumatoid states. *Ann NY Acad Sci* 168:30-38, 1969.

8. Hoiby N, Wiik A: Antibacterial precipitins and autoantibodies in sera of patients with cystic fibrosis. *Scand J Respir Dis* 56:38-46, 1975.

Congenital Miliary Tuberculosis Proved by Open Lung Biopsy Specimen and Successfully Treated

Congenital tuberculosis is a rare disease with a high mortality.[1-7] Fewer than 200 cases have been reported in the world literature; less than 100 in the United States.[2] The incidence is not known. A patient who was successfully treated is described.

Report of a Case.—The patient was a 3-kg product of a full-term pregnancy. During the first trimester, the mother suffered an illness consisting of fever, cough, and right-sided chest pain. Her condition was diagnosed as being pleurisy and bronchitis. The remainder of the pregnancy and the immediate postnatal period were uneventful. At 3 weeks of age, the baby was transferred to the Children's Hospital from an outlying hospital where he had been treated for five days for fever, cough, and anorexia.

The baby was lethargic. The rectal temperature was 38.5 °C. The respiratory rate was 40/min, the heart rate was 146 beats per minute, and the blood pressure was 60/40 mm Hg. The lungs were clear to auscultation. The liver was palpable 4 cm below the right costal margin. The spleen was felt 1 cm below the left costal margin. A WBC count was 18,200/cu mm, with 46% band forms, 44% polymorphonuclear leukocytes, and 8% lymphocytes. The hematocrit reading was 45. A platelet count was 144,000/cu mm. Urinalysis, electrolyte, blood urea nitrogen, and serum glucose test results were normal. The CSF was normal on two occasions. The lactate level of the second CSF was normal. A chest roentgenogram showed an extensive miliary infiltrate (Fig 1).

Viral cultures and tests for syphilis, toxoplasmosis, and rubella were negative. Serum immunoglobulin test, bone marrow aspirate, skeletal roentgenograms, and ophthalmoscopy showed no abnormalities. An abdominal roentgenogram showed moderate hepatosplenomegaly. An initial

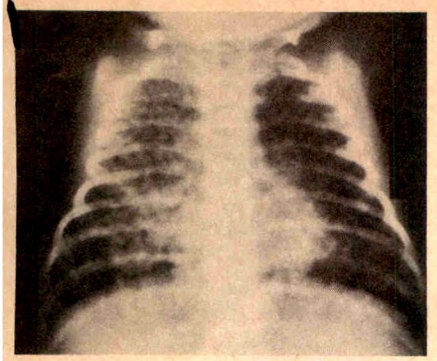

Fig 1.—Film of chest at 3 weeks of age.

Fig 2.—Lung biopsy specimen showing hypercellularity, subpleural alveolar obliteration, and proliferation of large histiocytic cells.

intradermal skin test using intermediate strength (5 TU) of purified protein derivative of tuberculin was negative at 48 hours.

A chest roentgenogram of the patient's mother showed pleural thickening on the right. At 48 hours, her tuberculin skin test was read as 15 mm of induration. The patient's father and brother had normal chest roentgenograms and negative skin tests. The mother was given isoniazid, 300 mg daily, by her local health department.

The day after admission, the baby was begun on a regimen of isoniazid, 15 mg/kg/day; streptomycin sulfate, 35 mg/kg/day; and rifampin, 15 mg/kg/day. An open-lung biopsy specimen at 5 weeks of age confirmed the diagnosis of miliary tuberculosis. Light microscopy showed areas of large histiocytes and lymphocytes (Fig 2). *Mycobacterium tuberculosis hominis*, niacin-positive, sensitive to isoniazid, grew from culture.

The patient's condition improved steadily during the remainder of his hospitalization, and he was discharged at 2 months of age. He has been followed up in the chest clinic at the Children's Hospital where his psychomotor development has been normal. A follow-up PPD at 6 months of age was positive (10-mm induration).

At 8 months of age, the patient's height, weight, and head circumference are at the 50th percentile. His physical examination showed no abnormalities. His chest roentgenogram shows substantial improvement. No calcifications have been identified to date in either the lungs or the liver. Results of liver function tests have remained normal.

Comment.—Congenital tuberculosis may be defined as an infection of the child with *M tuberculosis* contracted from the mother during intrauterine life. Avenues of infection include aspiration or ingestion of infected amniotic fluid and transplacental hematogenous spread through the umbilical vein to the fetal liver.[8] In 1935, Bietzke[9] proposed the criteria necessary to insure the congenital nature of the disease. These are as follows: (1) The diagnosis of tuberculosis must be proved in mother and child. (2) The infant must have a primary tuberculous complex in the liver. (This usually is demonstrable only if calcification appears roentgenographically.) (3) The lesions must be present in the first few weeks of life, or if points 2 and 3 are not fulfilled, then extrauterine infection must be excluded.

In the case reported, the probable route of infection was hematogenous, with infection of the infant via the umbilical vein. The age of onset (3 weeks), histologic findings of the lung, and the history of pleural effusion during the first trimester are all compatible with this route of infection. Furthermore, there were no other cases of tuberculosis found in the family. Unfortunately, no placental tissue was available.

Few survivors of congenital tuberculosis have been recorded.[10-11] Early and aggressive diagnostic and therapeutic measures are mandatory to improve survival. The disease must be suspected in infants with otherwise unexplained pulmonary disease, especially in those born to tuberculous mothers. Placentas from those pregnancies should, if possible, be examined histologically. Infants born to mothers with positive skin tests should receive extremely close observation and follow-up. When active tuberculosis is found during pregnancy, treatment may prevent transmission to the fetus.

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Nonproprietary Name and Trademarks of Drug

Rifampin—*Rimactane, Rifadin.*

1. Pai P: Congenital miliary tuberculosis. *Clin Pediatr* 15:376-378, 1976.
2. Hopkins R, Ermocilla R, Cassady G: Congenital tuberculosis. *South Med J* 61:1156, 1976.
3. Harris EA, McCullough GC, Stone JJ, et al: Congenital tuberculosis. *J Pediatr* 32:311-316, 1948.
4. Reisinger KS, Evans P, Yost G, et al: Congenital tuberculosis: Report of a case. *Pediatrics* 54:74-76, 1974.
5. Mickleson KN, Kirk GM: Congenital tuberculosis. *N Z Med J* 66:383-385, 1967.
6. Todd RM: Congenital tuberculosis: Report of a case with unusual features: *Tubercle* 41:71-74, 1960.
7. Voyce MA, Hunt AC: Congenital tuberculosis. *Arch Dis Child* 41:299-300, 1966.
8. Horley J: Congenital tuberculosis. *Arch Dis Child* 27:167-172, 1952.
9. Bietzke H: Uber die angeborene tuberkulose infektion. *Ergeb ges Tuberk Forsch* 7:1-30, 1935.
10. Davis SF, Finley SC, Hare WK: Congenital tuberculosis: Report of a case. *J Pediatr* 57:221-224, 1960.
11. Polansky SM, Frank A, Ablow RC, et al: Congenital tuberculosis. *Am J Roentgenol* 130:994-996, 1978.

Amantadine for Severe Influenza A Pneumonia in Infancy

Influenza A virus may cause severe illness in infancy.[1,2] Amantadine hydrochloride is effective as a prophylactic agent[3,4] and is free of serious side effects[5] when administered to older children. Although therapeutic field trials with amantadine have included children,[6] we are unaware of any attempts to treat serious illness caused by influenza A in childhood, nor are there dosage recommendations for children under 1 year of age.

Report of a Case.—A 5-month-old girl was admitted to Colorado General Hospital on Dec 21, 1977, with fever, cough, and tachypnea. Physical examination revealed otitis media and a seborrheic skin rash. A chest roentgenogram revealed diffuse interstitial infiltrates. In ambient oxygen, the Pao_2 was 38 mm Hg; the WBC count was 13,300/cu mm. She was treated with forced inspiratory oxygen (FIO_2) of 40% and received broad-spectrum antibiotics for presumed bacterial pneumonia and sepsis until cultures of blood, spinal fluid, and urine proved to be sterile. Increasing respiratory distress and worsening interstitial infiltrates led to the performance of a percutaneous needle aspiration of the left lung on Dec 29, 1977. Cultures of the aspirate fluid and the upper respiratory tract taken six days earlier grew influenza A virus (A/Vic/3/75). Methenamine silver-stained specimens of the aspirate fluid

revealed *Pneumocystis carinii*. The infant was treated with trimethoprim-sulfamethoxazole (20 mg/kg/day of trimethoprim) and, because of the gravity of her illness, with amantadine hydrochloride (2.5 mg/kg/12 hours), after informed consent was obtained. Both compounds were administered by nasogastric tube. She was placed on assisted ventilation, ultimately requiring an FIO_2 of 100% and end-expiratory pressures of 15 cm of H_2O. Abnormalities of hepatic, hemostatic, and neurologic function appeared; renal function remained normal. Because of the unusual combination of infectious agents, an immunological evaluation was performed, yielding a diagnosis of the syndrome of cellular immunodeficiency with immunoglobins[7] (M. Fishaut, MD, D. Tubergen, MD, K. McIntosh, MD, unpublished observations, 1978). She died on Jan 6, 1978. Microscopic examination of the lungs revealed hemorrhage and gross consolidation. Silver-stained specimens were positive for *P carinii*.

The needle aspiration fluid, respiratory secretions, and tissue specimens obtained at postmortem examination were inoculated into primary rhesus monkey kidney cell monolayers that were assessed for influenza virus by patterns of hemadsorption and cytopathic effect. Isolates were subtyped by hemagglutination inhibition.[8] Specimens were also titrated for infectivity in rhesus monkey kidney. Virus was cultured for 15 days with peak titers of $10^{5.5}$ tissue culture infective dose ($TCID_{50}$)/0.1 mL of secretion. All isolates were influenza A/Vic/3/75. Of the tissues from which specimens were obtained, virus was recovered only from the lung.

Amantadine concentrations, measured by a gas chromatographic electron capture technique, were determined from pooled sera, timed sera, a random urine specimen, and several tissue specimens obtained 4½ hours after the final dose. The concentrations of amantadine are summarized in the Table. Serum concentrations ranged from 0.80 μg/mL to 1.64 μg/mL. Higher concentrations were found in urine and in several tissues, particularly lung (21.40 μg/mL).

Amantadine Hydrochloride Concentrations in Serum, Urine, and Tissue Specimens

Date	Specimen	Amantadine Concentration, μg/mL
Dec 31, 1977	Serum	0.88
Jan 1, 1978	Serum	0.82
Jan 2, 1978	Serum	0.80
Jan 6, 1978	Serum	1.64 (predose)
Jan 6, 1978	Serum	1.54 (60 min postdose)
Jan 6, 1978	Urine	17.30
Jan 6, 1978	Lung	21.40
Jan 6, 1978	Liver	11.70
Jan 6, 1978	Kidney	2.40
Jan 6, 1978	Brain	1.70
Jan 6, 1978	Bone marrow	0.36

Comment.—Amantadine hydrochloride has been administered to an infant in an attempt to limit the excretion of rubella virus,[9] but the youngest child reported to have received amantadine for influenza A prophylaxis was 15 months old.[5] Little is known about the behavior of this compound in the very young. In young adults, amantadine administered as a single 4 mg/kg dose has been found to have a half-life of nine to 15 hours, with a peak plasma concentration of 0.5 μg/mL, and to be excreted unchanged in the urine.[9] Older patients chronically receiving 200 to 300 mg/day of amantadine achieve serum concentrations of up to 1.12 μg/mL with a half-life of 30 hours,[10,11] while a group of children and young adults with cystic fibrosis receiving 6 mg/kg/day for one month achieved mean blood concentrations of 0.6 μg/mL.[5]

We chose 5 mg/kg/day divided into two doses for our patient in whom normal renal function was maintained throughout the illness. The serum concentrations were comparable to those in older children and adults: despite the infant's overall ill health, the compound was well absorbed from the gastrointestinal tract. The terminal serum concentrations were slightly elevated but well below those at which toxicity has been observed.[12] Thus our dosage schedule, in the presence of normal renal function, seems a reasonable one for infants.

Tissue concentrations of amantadine have been reported previously only in rodents.[13] We observed an approximately fourteenfold concentration of amantadine in lung over serum concentration after seven days of therapy to a level that significantly inhibits the replication of many influenza A viruses, including A/Vic/3/75, in tissue culture.[14] In vivo virus replication was not inhibited, in spite of the high concentration of drug in the lung. However, this child did have underlying immunodeficiency, as well as infection with *P carinii*. Amantadine-resistant strains of influenza A have been described,[15] but we were unable to test our patient's isolate.

Although amantadine did not alter the course of this child's infection, observations have been made of positive effects in influenza A infection.[16] These observations, coupled with our observation of high drug concentrations in serum and lung despite overwhelming illness, suggest that amantadine might be useful in the treatment of severe influenza A infection in children.

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References

1. Brocklebank JB, Court SDM, McQuillin J, et al: Influenza A infection in children. *Lancet* 2:497-500, 1972.

2. Howard JB, McCracken GH Jr, Luby JB: Influenza A2 virus as a cause of croup requiring tracheostomy. *J Pediatr* 81:1148-1150, 1972.

3. Quilligan JJ Jr, Hirayama M, Baernstein HD Jr: The suppression of A2 influenza in children by chemoprophylactic use of amantadine. *J Pediatr* 69:572-575, 1966.

4. Galbraith AW, Oxford JS, Schild GC, et al: Protective effect of 1-adamantanamine hydrochloride on influenza A2 infections in the family environment. *Lancet* 2:1026-1028, 1969.

5. Wright PF, Khaw KT, Oxman MN, et al: Evaluation of the safety of amantadine HCl and the role of respiratory virus infections in children with cystic fibrosis. *J Infect Dis* 134:144-149, 1976.

6. Galbraith AW, Oxford JS, Schild GC, et al: Therapeutic effect of 1-adamantanamine hydrochloride in naturally occurring influenza A2/Hong Kong infection. *Lancet* 2:113-116, 1971.

7. Lawlor GJ, Amman AJ, Wright WC Jr: The syndrome of cellular immunodeficiency with immunoglobulins. *J Pediatr* 84:183-192, 1974.

8. Robinson RQ, Dowdle WR: Influenza viruses, in Lennette EH, Schmidt NJ (eds): *Diagnostic procedures for Viral and Rickettsial Infections*, ed 4. New York, American Public Health Association Inc, 1969, pp 414-433.

9. Plotkin SA, Kraus RM, Whitely JP: Hypogammaglobulinemia in an infant with congenital rubella syndrome: Failure of 1-adamantanamine to stop virus excretion. *J Pediatr* 69:1085-1091, 1966.

10. Greenblatt DJ, DiMascio A, Harmatz JS, et al: Pharmacokinetics and clinical effects of amantadine in drug-induced extrapyramidal syndromes. *J Clin Pharmacol* 17:704-708, 1977.

11. Rizzo N, Biandrate P, Tognoni G, et al:

Amantadine in depression: Relationship between behavioral effects and plasma levels. *Eur J Clin Pharmacol* 5:226-228, 1973.

12. Armbruster KFW, Rahn AC, Ing TS, et al: Amantadine toxicity in a patient with renal insufficiency. *Nephron* 13:183-186, 1974.

13. Bleidner WE, Harman JB, Hewers WE, et al: Absorption, distribution, and excretion of amantadine hydrochloride. *J Pharmacol Exp Therap* 150:484-490, 1965.

14. Oxford JS: Specific inhibitors of influenza related to the molecular biology of virus replication, in Oxford JS (ed): *Chemoprophylaxis and Viral Infections of the Respiratory Tract*. Cleveland, CRC Press, 1977, vol 1, pp 139-187.

15. Appleyard G: Amantadine resistance as a genetic marker for influenza viruses. *J Gen Virol* 36:249-255, 1977.

16. Little JW, Hall WJ, Douglas RG Jr, et al: Amantadine effect on peripheral airways abnormalities in influenza. *Ann Intern Med* 85:177-182, 1976.

Lidocaine Ingestion

Lidocaine hydrochloride is a useful local anesthetic and antiarrhythmic agent. Serious adverse systemic reactions to lidocaine are reported to be uncommon with parenteral dosage forms and extremely rare with the topical dosage form. We are reporting a case of accidental lidocaine (Xylocaine 2% viscous) hydrochloride ingestion resulting in seizures and respiratory arrest. We have found no other reported case of lidocaine 2% viscous ingestion in the literature.

Report of a Case.—A 22-month-old female infant, weighing 10 kg, ingested 20 to 25 mL of lidocaine 2% viscous, which had been prescribed because of stomatitis. She began convulsing at home and convulsed continually while her mother was bringing her to the emergency room. On arrival at the hospital, she was cyanotic and mottled in appearance, was convulsing intermittently, and had no respirations. She was observed to have a large quantity of mucus in her hypopharynx, and it was feared that she had aspirated stomach contents. Her heart rate was 160 beats per minute, and her systolic blood pressure was 160 to 180 mm Hg. A clear diastolic pressure could not be determined.

Blood analysis demonstrated a pH of 6.96, a P_{CO_2} of 106, a P_{O_2} of 85, a bicarbonate-ion concentration of HCO_3 of 23 mM/L, with a base excess of −12. This sample was taken after she had been intubated and was being ventilated with oxygen. Her WBC count was 13,200/cu mm, with 16% polymorphonuclear cells and 84% lymphocytes. Results of urinalysis were normal.

The patient was successfully resuscitated, and her seizures were controlled with intravenous (IV) diazepam. Her respiratory status was stable 1½ hours after arrival at the hospital, and she was transferred to the intensive care unit. During the next 12 hours, she was mildly febrile, with a temperature of 39 °C. Hemodynamics remained stable, and she demonstrated no arrhythmias. Twenty-four hours after admission, she was afebrile and alert, and she was transferred to the general pediatric ward. She was discharged 48 hours after admission.

Follow-up.—The patient, now 3 years old, seems to have suffered no developmental sequelae as a result of this incident.

Comment.—Lidocaine is well absorbed through the mucous membranes and from the gastrointestinal tract. Only about 35% of an oral dose reaches the systemic circulation because lidocaine undergoes extensive hepatic metabolism.[1] Some investigators have indicated that the metabolite is pharmacologically active and may in fact be partly responsible for some of the toxic effects.[1] Lidocaine rapidly distributes into tissues and is then eliminated from the serum at a relatively slower rate, with a serum half-life of one to 1½ hours.[2] After oral administration, peak serum concentrations are seen in 30 to 60 minutes.[1] There is a correlation between serum concentration and adverse reactions.[3] The CNS adverse reactions usually predominate, but cardiovascular adverse reactions may also be seen when high serum concentrations are achieved. Symptoms of lidocaine toxicity include drowsiness, dizziness, paresthesias, muscle twitching, dysarthrias, blurred vision, vomiting, hypotension, bradycardia, respiratory arrest, convulsions, and death.[1,3-7] Our patient interestingly had both hypertension and tachycardia. Lidocaine depresses the cough reflex.[8] Cohen and Levinsky,[9] in 1976, reported an adult case of aspiration secondary to lidocaine viscous therapy. The prescribed dose in that case was only 5 mL before meals.

Our patient ingested approximately 25 mL of a 2% solution or 50 mg/kg of lidocaine. Assuming 35% reaches the systemic circulation after oral ingestion, 17.5 mg/kg reached the systemic circulation in this patient. The recommended IV antiarrhythmic dose is 1 to 5 mg/kg by IV bolus to be followed by a 10 to 50 μg/kg/min continuous infusion to maintain therapeutic serum concentrations.[10] Thus, approximately 3½ times the maximum recommended IV loading dose reached the systemic circulation after oral ingestion in this patient.

Conclusion.—Physicians prescribing lidocaine 2% viscous should know that 25 mL may result in serious adverse reactions, as exemplified in our patient. Lidocaine 2% viscous now has a safety cap, but old stock lacking a safety cap may still be available in some wholesale houses, pharmacies, and scattered medicine cabinets throughout the country.

Based on absorption data and the kinetics of lidocaine, one can predict that toxicity will be seen soon after ingestion and will peak in 30 to 60 minutes. Improvement should be seen two to three hours after ingestion, and the adverse symptoms should disappear by 12 to 24 hours in patients with normal renal and hepatic function. Therapy should include (1) discontinuation of further exposure to lidocaine; (2) maintenance of adequate respiratory status; and (3) treatment of seizures, if present, with anticonvulsants. Lidocaine 2% viscous toxicity is not common, but careful supportive treatment must be started promptly. With supportive treatment, adverse symptoms subside soon after ingestion.

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1. Boyes RN, Scott DB, Jebson PJ: Pharmacokinetics of lidocaine in man. *Clin Pharmacol Ther* 12:105-116, 1971.

2. Thomson PD, Melmon KL, Richardson JA, et al: Lidocaine pharmacokinetics in advanced heart disease, liver disease, and renal failure in humans. *Ann Intern Med* 78:499-508, 1973.

3. Rosen MR, Hoffman BF, Wit AL: Electrophysiology and pharmacology of cardiac arrhythmias: V. Cardiac anti-arrhythmic effect of lidocaine. *Am Heart J* 89:526-536, 1975.

4. Pfeifer HJ, Greenblatt DJ, Koch-Weser J: Clinical use and toxicity of intravenous lidocaine. *Am Heart J* 92:168-173, 1976.

5. Reilly MJ: *American Hospital Formulary Service*. Washington, DC, American Society of Hospital Pharmacists, 1978, vol 24, p 4.

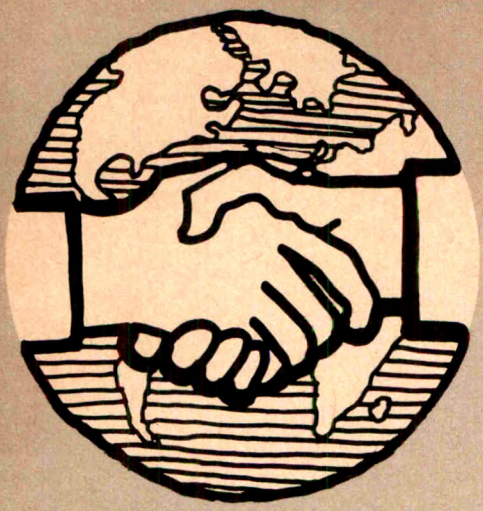
6. Eisinger AJ, Hellier MD: Oral lignocaine. *Lancet* 2:1303, 1969.

7. Parkinson PI, Margolin L, Dickson DSP: Oral lignocaine: Its absorption and effectiveness in ventricular arrhythmia control. *Br Med J* 2:29-30, 1970.

8. Smith FR, Kundahl PC: Intravenously administered lidocaine as cough depressant during general anesthesia for bronchography. *Chest* 63:427-429, 1973.

9. Cohen MR, Levinsky WJ: Topical anesthesia and swallowing. *JAMA* 236:562, 1976.

10. Gelband H, Rosen MR: Pharmacologic basis for the treatment of cardiac arrhythmias. *Pediatrics* 55:59-67, 1975.



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WARNING

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

Indications: *Streptococcus pyogenes* (Group A Beta-Hemolytic) – Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity.

Injectable penicillin G benzathine is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient's strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least ten days.

Alpha-Hemolytic Streptococci (Viridans Group) – Short-term prophylaxis against bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin. (Erythromycin is not suitable prior to genitourinary surgery when the organisms likely to lead to bacteremia are gram-negative bacilli or belong to the enterococcus group of streptococci.)

Staphylococcus aureus – Acute infections of skin and soft tissue which are mild to moderately severe. Resistance may develop during treatment.

S. (Diplococcus) pneumoniae – Infections of the upper respiratory tract (e.g., otitis media, pharyngitis) and lower respiratory tract (e.g., pneumonia) of mild to moderate severity.

Mycoplasma pneumoniae (Eaton Agent, PPLO) – Respiratory tract infections due to this organism.

Haemophilus influenzae – May be used concomitantly with adequate doses of sulfonamides for upper respiratory tract infections of mild to moderate severity. Not all strains of this organism are susceptible at the erythromycin concentrations ordinarily achieved.

Treponema pallidum – As an alternate treatment in penicillin-allergic patients. In primary syphilis, spinal-fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae – As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

C. minutissimum – In the treatment of erythrasma.

Entamoeba histolytica – For intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes – Infections due to this organism.

Legionnaires' Disease – Although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Contraindication: Known hypersensitivity to this antibiotic.

Warnings: (*See* Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy – Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Recent studies of erythromycin reveal that its use in patients receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In such a case, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, overgrowth of nonsusceptible bacteria or fungi is possible. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported. [013079]

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

See adjoining column for summary of prescribing information.

Letters to the Editor

Pediatrics and Record-keeping

Sir.—I appreciated the careful study of the use of ambulatory medical records reported by Margolis and Porter (JOURNAL 132:1115-1116, 1978). Although their observations are clearly presented, I had thought that the responsibility of the pediatrician at any acute ambulatory visit would involve review of the patient's total health status. Identification of chronic health problems and their current condition, review of health problems identified at the last visit or by telephone during the interval, determination of immunization status and currentness of preventive health care, inquiry regarding additional health problems, and identification of the time of the next appropriate ambulatory visit would be included. Furthermore, recurrent health problems are so much the rule in pediatrics that, except in the setting of the occasional emergency room visit, it would seem to me that the time expended in identifying the case with a nonrecurrent problem would outweigh the saving achieved by not pulling the record. Even in the apparently nonrecurrent problem, in my own office, where charts are regularly reviewed both at office visits and when emergency room copies are received, previous similar pathology or contributory problems in areas such as allergic, developmental, social, and emotional disturbance are frequently found.

I would hope that the report by Drs Margolis and Porter would not discourage those seeking to eliminate fragmentation in ambulatory pediatric care. Particularly in these days, when young families' roots are not always strong and when medical science is increasingly complex and changing, young patients and their parents need the assurance provided by a medical home, so medical care may be comprehensive and well coordinated.

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In Reply.—Dr Sparling is misinterpreting our report if he believes that we are trying to detract from the importance of comprehensive care. His reservations may be related to the differences in the practice setting: the prepaid health insurance system that covers more than 90% of all the patients in our study results in a high number of visits per annum, compared with the number of visits in a fee-for-service operation. If most of our patients see the pediatrician on an average of six times per year (as well as separate "well baby" visits to a preventive-medicine nurse four to five times in a year), then review of the patient's total health status at each visit is simply not necessary. So, we could certainly add that our conclusions are conditional on periodic comprehensive appraisal of the patient's problem list, at separate visits.

If our differences of opinion are not related to practice setting, then we do not agree that every acute visit demands a comprehensive review. In our opinion, no primary care setting that provides acute care can afford to give comprehensive care at the same time.

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Recurrent Abdominal Pain

Sir.—What causes recurrent abdominal pain in children? And what should pediatricians do about it?

If a comprehensive battery of the usual studies (such as a complete blood cell count, urinalysis, ESR, examination of the stool for ova and parasites, and gastrointestinal (GI) roentgenograms show no abnormalities, what then? Should the patient be referred for psychiatric counseling because nothing "organic" has been found? Or should he undergo even more extensive testing and study, including EEG, rectal biopsy, sigmoidoscopic examination, or exploratory laparotomy?

Or could there be a simpler answer for a child's problem? A simpler diagnostic test, such as the elimination diet?

In the past 17 months, two separate articles with the identical title, "Recurrent Abdominal Pain," have appeared in the JOURNAL (131:1340-1344, 1977 and 133:486-489, 1979). One study consisted of a review of the management of 19 patients, while the other was a long-term follow-up study of 161 children. In both of these reports, the authors said, in effect, "When the usual studies show no organic cause for a child's recurrent abdominal pain, we approach the problem from the emotional point of view." Moreover, the references cited in each of these reports included publications that presented an identical point of view. Yet they ignored the possibility that recurrent abdominal pain may be caused by adverse or allergic reactions to food, especially cow's milk.

Through the years, a number of physicians have pointed out that recurrent abdominal pain can be a manifestation of hidden, masked, nonreaginic, or delayed-onset food allergy and a cardinal symptom of "food toxemia" or the allergic tension-fatigue syndrome.[1-6] Moreover, a recent report indicates that lactose intolerance may also play an important role in causing recurrent abdominal pain even though other GI symptoms are absent.[7]

To determine whether or not a child's recurrent abdominal pain is caused by an adverse or allergic reaction to one or more foods requires the following: (1) awareness that such food-induced reactions occur; (2) recognition of the symptoms that characteristically accompany food-induced abdominal pain, including pallor, infraorbital circles, nasal stuffiness, headache, limb pain, fatigue, and mental and emotional symptoms; and (3) carrying out, by the patient, of a carefully planned elimination diet lasting from seven to 21 days, followed by challenges to determine the food offenders. Although I do not claim to understand all of the mechanisms involved in such reactions, in my experience during the past 23 years of general pediatric and allergy practice, adverse or allergic reactions to common foods have been the most frequent cause of chronic complaints among my patients.

Physicians and other professionals who would like a copy of the elimina-

tion diet I use may obtain it by sending me a stamped, self-addressed envelope.

WILLIAM G. CROOK, MD
The Children's Clinic
657 Skyline Dr
Jackson, TN 38301

1. Bullock JD, Deamer WC, Frick OL, et al: Recurrent abdominal pain. *Pediatrics* 46:971-972, 1970.

2. Crook WG, Harrison WW, Crawford SE, et al: Systemic manifestations due to allergy: Report of 50 patients and a review of the literature on the subject (allergic toxemia and the allergic tension-fatigue syndrome). *Pediatrics* 27:[illegible], 1961.

3. Deamer WC: Pediatric allergy: Some impressions gained over a 37-year period. *Pediatrics* 48:930-938, 1971.

4. Gerrard JW: *Understanding Allergies.* Springfield, Ill, Charles C Thomas Publisher, 1973.

5. Deamer WC: Recurrent abdominal pain: A frequent manifestation of food allergy. *Curr Med Dialogue* 40:130-154, 1973.

6. Crook WG: Food allergy: The great masquerader. *Pediatr Clin North Am* 22:227-238, 1975.

7. Barr RG, Levine, MD, Watkins, JB: Recurrent abdominal pain of children due to lactose intolerance. *N Engl J Med* 300:1449-1452, 1979.

In Reply.—In 26 years of practice during which I have seen many children with abdominal pain and the so-called tension-fatigue syndrome (headaches, infraorbital circles, limb pain, and so forth), I have yet to substantiate "milk allergy" as the basis for the complaints. Although a large body of empirical information repeatedly emphasizes the importance of milk allergy, I believe that we in the medical profession should take a firm stand against such empiricism by demanding carefully *controlled* studies of the problem.

Recently at our institution, Charles D. May, MD, presented his views about food allergy. He stated, "Proof that a food causes an adverse reaction and that the manifestations are not psychologic in origin is obtained with a food challenge."[1] Only patients with symptoms suggesting an anaphylactic reaction need not undergo a double-blind challenge. In cases of suspected food allergy, May demands that the offending food be placed in a capsule and that the patient be given either a placebo or the possibly allergenic food in this capsule. Neither the patient nor the observer should know whether the allegedly offending food is given. If the reaction is positive, this verifies a relationship between ingestion and an ill effect, but it does not provide information about the presence or absence of an immune mechanism or the involvement of the immune mechanism. If an IgE-mediated adverse reaction is suspected, properly performed skin testing[2] and the radioallergosorbent test may be useful ancillary diagnostic studies.[3-5]

It would be foolish to state that there is no such thing as food allergy; indeed, there are excellent and well-proved examples. However, the assumption that the use of milk is associated with widespread food allergy is a faddist belief, which is being adopted by an increasing number of physicians. Because of such beliefs, the use of soy formulas has increased. Possibly, the fear of milk allergy has created anxiety rather than promoting useful therapeutic management. If Dr Crook can demonstrate by carefully controlled studies that milk allergy, indeed, causes abdominal pain, I certainly would be grateful.

In our long-term follow-up study, we did not find a single patient who proved to have milk allergy, and our approach to managing the school phobia in these patients resulted in a substantial cure rate. We realize that this approach is also empirical, but thus far, no one has found a method of designing controlled studies for psychosomatic disorders. We are aware of the study in Boston by Barr et al (Dr Crook's reference 7), but we are concerned about the absence of controls in their study. Because psychosomatic abdominal pain is such a frequent condition (namely, one in nine schoolchildren have it), it would not be unusual to find lactose intolerance in patients who have true school phobia. The latter needs to be studied further; routine exclusion of lactose intolerance in patients with recurrent abdominal pain may be necessary. Never did we suggest studies or procedures such as electroencephalography, rectal biopsy, or sigmoidoscopy as part of a routine examination for patients with recurrent abdominal pain, and we emphatically oppose the use of exploratory laparotomy.

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Rochester, MN 55901

Dr Berger declined to reply.—ED.

1. May CD, Bock SA: Adverse reactions to food due to hypersensitivity, in Middleton E Jr, Reed CE, Ellis EF (eds): *Allergy: Principles and Practice.* St Louis, CV Mosby Co, 1978, vol 2, pp 1159-1171.

2. May CD: Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol* 58:500-515, 1976.

3. Hoffman DR, Haddad ZH: Diagnosis of IgE-mediated reactions to food antigens by radioimmunoassay. *J Allergy Clin Immunol* 54:165-173, 1974.

4. Chua YY, Bremner K, Lakdawalla N, et al: In vivo and in vitro correlates of food allergy. *J Allergy Clin Immunol* 58:299-307, 1976.

5. Gillespie DN, Nakajima S, Gleich GJ: Detection of allergy to nuts by the radioallergosorbent test. *J Allergy Clin Immunol* 57:302-309, 1976.

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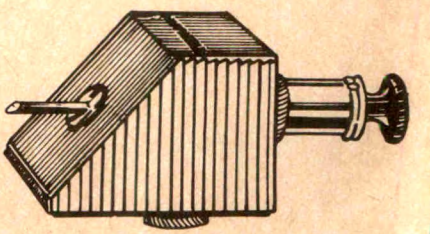
An Improved Needle for Sinus Therapy

Used extensively in the Babies' Hospital for "intravenous administration of arsphenamin, physiologic sodium chloride solution, glucose and sodium bicarbonate solution as well as for withdrawal of blood for diagnostic purposes," the author invented the needle set-up pictured. It represents an improved method of puncturing the sagittal sinus, was considered safer than one previously employed which entered at a 90 degree angle and could readily puncture the opposite wall of the sinus or cerebral cortex.

The sagittal sinus is entered immediately forward of the posterior angle of the anterior fontanelle. For young infants 4 to 6 millimeters of needle is used; 5 to 8 millimeters for older ones.—Alton Goldbloom, MD, Babies' Hospital, New York (19:229, March 1920).



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Brief Summary

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Indications: *Streptococcus pyogenes* (Group A beta hemolytic streptococcus)—Upper and lower respiratory tract infections, skin, and soft tissue infections of mild to moderate severity, where oral medication is preferred. Therapy should be continued for 10 days.

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S. aureus—Acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

S. pneumoniae (D. pneumoniae)—Upper and lower respiratory tract infections of mild to moderate degree.

M. pneumoniae—For respiratory infections due to this organism.

Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity when used concomitantly with adequate doses of sulfonamides. Not all strains of this organism are susceptible at the erythromycin concentrations ordinarily achieved (see appropriate sulfonamide labeling for prescribing information).

Treponema pallidum—As an alternate treatment in patients allergic to penicillin.

C. diphtheriae and C. minutissimum—As an adjunct to antitoxin. In the treatment of erythrasma.

Entamoeba histolytica—In the treatment of intestinal amebiasis.

L. monocytogenes—Infections due to this organism.

Legionnaires' Disease—Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

Establish susceptibility of pathogens to erythromycin, particularly when *S. aureus* is isolated.

Contraindications: Known hypersensitivity to erythromycin.

Warnings: Safety for use in pregnancy has not been established.

Precautions: Exercise caution in administering to patients with impaired hepatic function. There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving oral erythromycin products. Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In cases of theophylline toxicity and/or elevated serum theophylline levels the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy. Surgical procedures should be performed when indicated.

Adverse Reactions: Dose-related abdominal cramping and discomfort. Nausea, vomiting, and diarrhea infrequently occur. During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. Mild allergic reactions such as urticaria and other skin rashes may occur. Serious allergic reactions, including anaphylaxis, have been reported.

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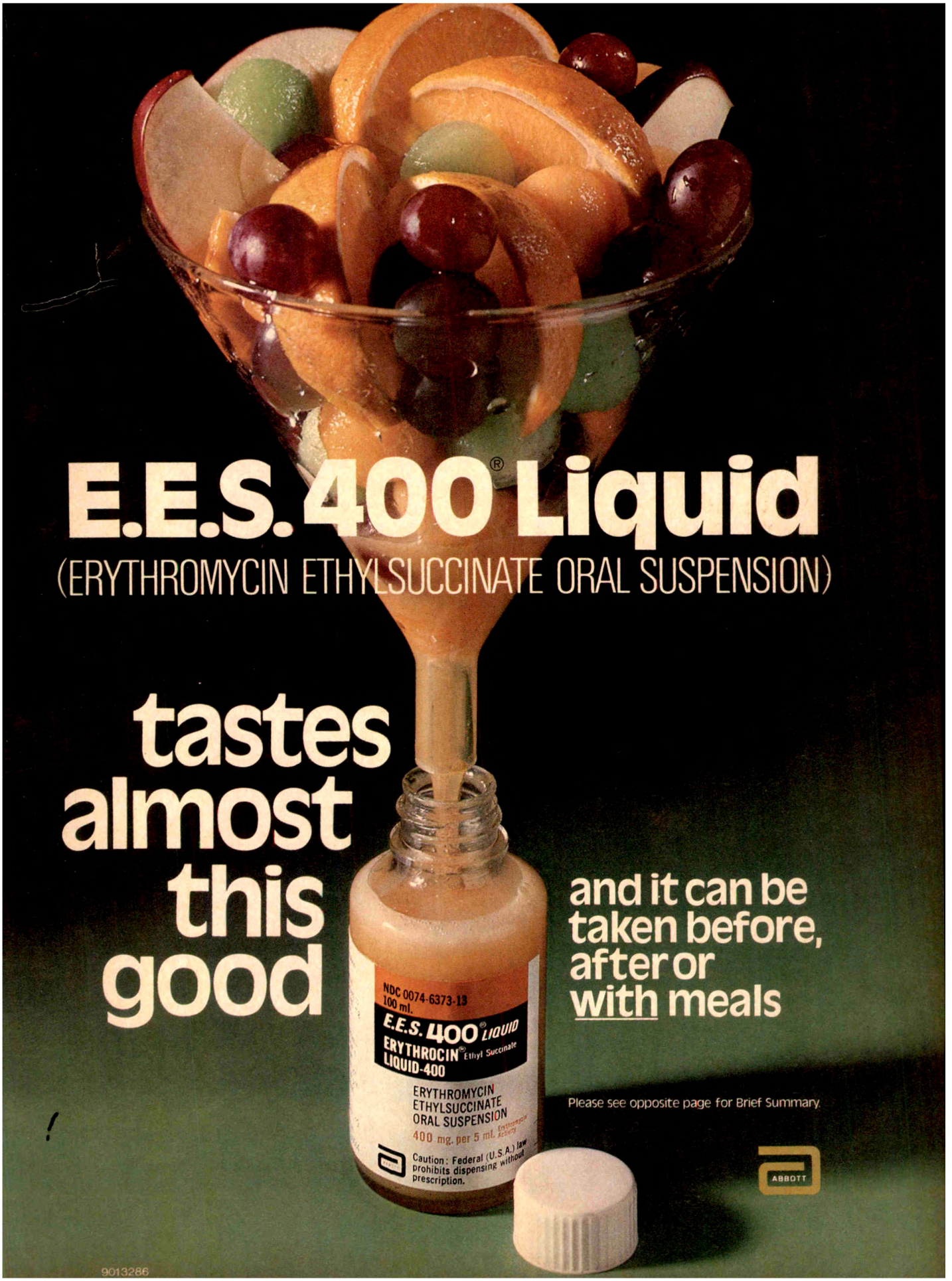
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How to Write and Publish a Scientific Paper, by Robert A. Day, 160 pp, $15 (hardcover), $8.95 (paperback), Philadelphia, ISI Press Inc, 1979.

In exchange for freedom of inquiry, scientists are obliged to explain their work.

CARL SAGAN

It is clever, of course, to be clever
And good, of course, to be good
But when you're so frightfully clever
As seldom to be understood
It's sad, though if anything sadder
Not to be quite as good as you should.

LEWIS CARROLL

As you record your experiments, do you compose your manunscript as a murder mystery waiting until the last paragraph of the discussion section for the denouement? Do you clutch to your breast the fine details of your experimental technic so your colleagues cannot reproduce them? Do you write in the text each and every detail of the tables in the event that they are not read properly? Do you imply the fact that the results of your study on five rats will be a turning point in your field or, conversely, are you afraid to discuss the implications of your study?

Robert Day offers some very practical suggestions for dealing with these problems. In a witty and direct style he describes how to write clearly each section of a manuscript—Introduction, Materials and Methods, Results, and Discussion—and how to prepare readable tables and figures. Selection of a journal appropriate to your type of study and the most appropriate methods of dealing with editors, and if your lucky, printers is reviewed.

This book is only 160 pages in length consequently, the chapters on proper style, syntax, spelling, and avoiding jargon are unfortunately limited for brevity's sake.

Now that you have read this far, you should have detected at least ten common errors in my style, spelling, punctuation, and use of jargon. If these errors are not obvious to you, do not waste any more time before you pick up this brief, delightful, and informative effort to improve the art of scientific communication. While your interest in these matters is piqued, please read on in a recently updated classic by Strunk and White[1] and consult frequently Bernstein's entertaining and enlightening volume on "The Careful Writer".[2] If you're the stubborn type and think such views are shared by only a few, read further with Flesch[3] and the Stylebook.[4]

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1. Strunk W Jr, White EB: *The Elements of Style*, ed 3. New York, Macmillan Publishing Co Inc, 1979.
2. Bernstein TM: *The Careful Writer: A Modern Guide to English Usage*. New York, Atheneum, 1977.
3. Flesch R: *The Art of Readable Writing*. New York, Macmillan Publishing Co Inc, 1962.
4. Scientific Publications Division, American Medical Association: *Stylebook: editorial manual of the AMA*, ed 6. Littleton, Mass, PSG Publishing Co Inc, 1976.

Haemorrhage, Ischaemia and the Perinatal Brain, by Karen E. Pape and J. S. Wigglesworth, 196 pp, $25, London, Spastics International Medical Publications, 1979.

Interest in the cerebral vasculature of the neonate has steadily increased as the success of modern perinatal care decreases mortality and morbidity for infants of all birth weights. Physicians have increasingly realized that many newborns die of intracranial vascular accidents and that the morbidity of those who survive is frequently related to vascular lesions producing neurological damage. Indeed, nearly one half of infants born prior to 32 weeks' gestation have some degree of intracranial hemorrhage depicted on computerized axial tomographic scans. In this book, the authors focus on the two major mechanisms by which the brain is most frequently damaged in the newborn, hemorrhage and ischemia. These mechanisms are examined from multiple aspects in an effort to prepare the reader for what Dr G Avery calls in the introduction "... a new era in the intensive care of the brain of the small premature."

The authors are both qualified specialists, who bring differing perspectives to this complex subject. Dr Pape is a neonatologist with experience in neurodevelopment, and Dr Wigglesworth is a pathologist. Both have worked in this field for many years and have published original work on neurological lesions in the newborn. Their combined expertise has produced a text that interrelates many facets of neonatal cerebral vasculature and provides the reader with multiple perspectives on this fascinating subject.

The book begins with a look at the economic importance of intracranial hemorrhage and ischemia. In the introductory chapter, the authors state these processes "now account for a high proportion of all neonatal mortality and permanent neurological handicap." After this, chapter 2 examines the cerebral blood supply to the developing brain. Here the authors discuss their own detailed anatomical studies of cerebral vasculature in the developing brain between 24 and 40 weeks' gestation. They emphasize the vascularity of the germinal matrix and its extensive capillary bed during the 24- to 28-weeks' gestational period, along with the striking proliferation of cortical vascularity after 32 weeks' gestation. This original work is excellent, is illustrated by superb photographs, and lays a solid foundation for the discussions that follow. Other chapters then examine the physiology of cerebral circulation, classification of cranial hemorrhage, hemorrhagic lesions, and other aspects of the problem as they relate to the newborn. The chapters are well researched, clearly written, and contain excellent references and illustrations.

The authors' working model of how cerebral vasculature is controlled includes a proposed mechanism for ischemic lesions. Throughout the text, there is scattered discussion of ischemia, but the emphasis is mainly on hemorrhagic lesions. The authors have successfully pulled together a variety of studies and provide the

reader with a broad background for understanding the anatomical and physiological basis for CNS damage in the neonate. They not only provide new material of their own, but they also prepare the reader for a better understanding of the studies that are now appearing in journals. The book can be highly recommended to anyone dealing with newborns, especially those who care for preterm infants.

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Pediatric Burns, edited by Wm. Carl Biley, 150 pp, Chicago, Year Book Medical Publishers Inc, 1979.

The text has been prepared from papers presented at the Fourth Annual Burn Symposium conducted by the Burn Team of the Children's Hospital, Denver. It consists of 11 chapters prepared by 15 authors, and deals with special problems encountered in the care of children with burns. The text emphasizes that children are not miniature adults and have special physiological and psychological needs. Each chapter begins with a statement of objectives and concludes with a self-evaluation quiz. Answers to the quiz are provided at the end of the book. The book is approved as a home study textbook meeting the criteria for 12 credit hours in category 1 for the Physician's Recognition Award of the American Medical Association.

Chapter 1 considers metabolic problems of burned children. In discussing fluid resuscitation, the author agrees with Baxter that the use of colloid is not necessary in the first 36 to 48 hours. He also considers different formulae for fluid resuscitation and concludes that the Parkland formula using 4 mL/kg per percent of body surface burned is appropriate. My own experience has been that use of the Parkland formula in both children and adults produces significant edema and fluid overload. A more appropriate level has been 3 mL/kg per percent of body surface burned. Metabolic effects of the burn that are accentuated in children are increase in evaporative water loss, elevated core temperature, increased metabolic rate and oxygen consumption, and increased catecholamine output. A discussion of the role of prostaglandins is presented and emphasis is placed on the increased nutritional needs of the burned child.

Chapter 2 is on pulmonary injury. The author describes the types of burns sustained by children and their effect on the respiratory system. Priorities for the evaluation and maintenance of the airway are reviewed. Factors that govern the cause and treatment of direct and indirect pulmonary injuries are outlined, as well as the symptoms, treatment, and mechanism of injury due to carbon monoxide poisoning. The author emphasizes that there is no evidence that corticosteroids reduce edema secondary to thermal injury and, indeed, they are contraindicated in burns that result from combustion of hydrocarbons. Causes of pulmonary infection are discussed and emphasis is placed on the maintenance of aseptic technique. Continued observation for respiratory failure is essential because treatment modalities may have significant respiratory consequences.

Chapter 3 deals with the diagnosis and control of sepsis. The cause and management of major sources of sepsis (ie, pulmonary, wound, and intravenous catheters) is discussed. Emphasis is placed on early debridement and the use of topical antimicrobial agents to control sepsis. Areas of controversy discussed are prophylactic systemic antibiotics, subeschar injection of antibiotics, excisional therapy at the time of sepsis, tangential excision, and the use of isolation techniques and laminar flow. With regard to prophylactic antibiotics, I agree that penicillin should not be used in the early phases of resuscitation, but that it should be used in the phase of grafting.

Chapter 4 is on the use of topical agents. The advantages and disadvantages of the various topical antimicrobials are outlined. Guidelines for selection of the topical agent and the treatment of various types of burns are given. The excellent eschar penetration of mafenide acetate is emphasized.

Chapters 5 and 6 deal with the problems of flammable fabrics. Factors that must be present for material to burn are outlined. The role of flame-retardant garments is discussed and emphasis is placed on the need for close supervision of activities of young children. The role of federal laws and regulations by the Consumer Protection Agency governing flame-retardant fabrics is outlined and, also, control of chemical toxicity of substances used to treat flame-retardant fabrics. Characteristics of the two types of flame-resistant fabrics are presented.

Chapter 7 is devoted to nursing care of the burned child. It is a detailed chapter designed to provide the nurse with specific guidelines and information for the administration of care to any burned person. Specific sections are devoted to those special considerations necessary for the care of a burned child. The chapter is the longest of the symposium, is very well organized, and presents the nursing care of the burned child within the framework of basic physiologic principles. It outlines in detail the anatomy and physiology of the skin, guidelines for estimation of the depth of burn and relationship of depth of burn, extent of burn, and medical history to burn survival. A careful outline of wound care is included.

Chapters 8 and 9 discuss the role of the child psychiatrist and social worker in the care of the burned child. The stages of hospitalization are outlined and the effects on the family in each of the stages are discussed. The stages presented are (1) impact, (2) recoil, and (3) restitution. The second stage of recoil is the most difficult. This is the stage when fear, guilt, and anger surface. Depression may also occur during this stage. It is emphasized that children who sustain burns tend to have had more problems prior to burn than are normally found in children. Also stressed is the fact that interaction between patients is helpful. It seems that children do better in their own environment rather than in an adult burn environment. I have not found this to be of particular importance in my own experience.

The social worker is primarily involved with the dynamics of the family crisis when the burn occurs and planning the long-term follow-up when the patient returns to the community. The crisis period is discussed in some detail.

Chapter 10 deals with the nurse-family relationship. The role of the nurse is defined, the concept of a support system in the nurse-family interaction is outlined, and the mechanisms to relate the support system or network to the role of the nurse in the nurse-family relationship is stressed. As a coordinator of care, the nurse

deals not only with the family, but with all members of the burn team.

The final chapter discusses the reconstructive problems of the burn patient. The indications for reconstruction are (1) contracture, (2) ulceration, and (3) appearance. Improvement of function assumes top priority. However, a most difficult problem is to maintain realistic expectations on the part of the patient and doctor about the final appearance of the patient. Techniques of skin grafting are discussed and problems related to reconstruction of specific anatomic areas are outlined. Special sections deal with electrical burns of the mouth and full thickness burns. Emphasis is placed on the fact that surgery of burn patients is not only technical, but also psychotherapeutic.

This book on pediatric burns is a useful addition to the library of any member of the pediatric burn team. It should be emphasized that it is not a textbook of burn therapy, but rather explores issues peculiar to the care of burned children.

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Histology of the Fetus and Newborn, by Marie Valdes-Dapena, 654 pp, with illus, Philadelphia, WB Saunders Co, 1979.

For the pathologist, it is often difficult to interpret pathologic findings from infants because of the difference in the histologic structures that these immature organisms display. More difficult still is the assessment of the degree of maturity in premature infants or in stillborns. Such differential diagnosis may be critical for the correct interpretation of growth retardation and certain congenital anomalies. Although sporadic papers on certain aspects of the histologic development exist and the topic finds superficial treatment in some pathology texts, no comprehensive work exists to aid the pathologist in his task.

This, then, is a welcome addition to our libraries. From her vast experience with perinatal pathology, Dr Valdes-Dapena has carefully selected a plethora of relevant pictures to document the structure of all organs in the human infant. The book is divided into 14 organ systems and 34 chapters. Each chapter is introduced by a succinct embryologic history of the organ, which is followed by a brief anatomical consideration. This is followed by a description of the salient histologic features. The photographs are carefully chosen and documented, with such data as fetal weight, race, sex, gestational age, and length of survival. The excellence of the more than 500 histologic preparations must be admired. There is not a wrinkle in the sections, they are uniformly stained, well photographed, and show no postmortem autolytic changes. The black-and-white photographs are crisp and readily allow recognition of the features that are critical to the understanding of the organ's principal features. Of particular value to pathologists will be the finer details of the developmental changes that take place in the lung, kidney, and CNS. Similarly, such features as extramedullary hematopoiesis in various organs, the sequential changes that occur in endocrine organs, the ciliation of esophageal epithelium, and many other special structures of the developing fetus are well depicted. Although only few references are appended to each chapter, they are carefully chosen and suffice to gain access to the relevant literature. But such should rarely be necessary, as this is an all-encompassing treatise.

Dr Valdes-Dapena has rendered a great service to the training programs of pathologists by documenting the perinatal histology of the developing human organism most comprehensively. Pathologists should find the book very helpful in the interpretation of difficult material. The book will find a welcome home in all pathology departments and is strongly recommended to all who have an interest in the interpretation of perinatal pathologic material.

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The Parents' Medical Manual, by Glenn Austin, Julia Stone Oliver, and John C. Richards, 426 pp, $8.95 (paperback), $15.95 (hardcover), Englewood Cliffs, NJ, Prentice-Hall Inc, 1978.

Of modest size and pleasing format, this book is an excellent guide and reference for educated parents concerning medical problems of children. The authors state in the preface that more than 400 physicians were consulted in deciding what to include in the book, and they have succeeded in including an explanation for, and the home treatment of, most common illnesses of childhood. It is hoped that sales will not be curtailed by a most unfortunate dust jacket. Prevention is stressed, not only in the first chapter entitled "Preventing Accidents and Poisonings," but throughout the book.

On seeing a listing of 70 contributing authors for a book of about 400 pages, one fears finding a hodgepodge of writing styles and a variability in quality of chapters. Such is not the case here as the contributions are distributed fleetingly in the text, sometimes in a few sentences and at other times in several pages. These contributions have been edited for smoothness. An example of how this works is seen at the outset of the chapter entitled, "The Mouth and Its Contents: Teeth and Braces, Thumb or Pacifier!" The author writes, "I asked my dentist, Dr. Frank McDaniel, DDS, 'How can you prevent dental bills?' He responded with the following advice." What follows is two clearly written pages on dental care of children. This unusual method of using edited contributions is skillfully done.

A contributing author is credited with the writing of only one chapter of the 22 in the book. Claude Frazier, MD, the pediatric allergist, has a chapter entitled "Stinging, Biting and Pesky Insects." There are some interesting photographs here as well as in some other chapters, and line drawings are used effectively throughout the book.

Organization of the material in this work deserves praise. Part I, entitled "Basic Home Health Responsibilities," is followed by "Illness: The Location," consisting of 11 chapters. This in turn is followed by six chapters on "Illness: The Cause." Part 4 is a group of "Medical Lists," including such things as information on poisonous plants; minerals and vitamins; food, drug, and cosmetic additives; a gluten diet.

The senior author, Glen Austin, a practicing pediatrician in Los Altos, Calif, worked on this book for five years. He deserves thanks from colleagues who may find their daily tasks a little easier if parents use it.

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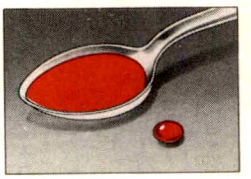

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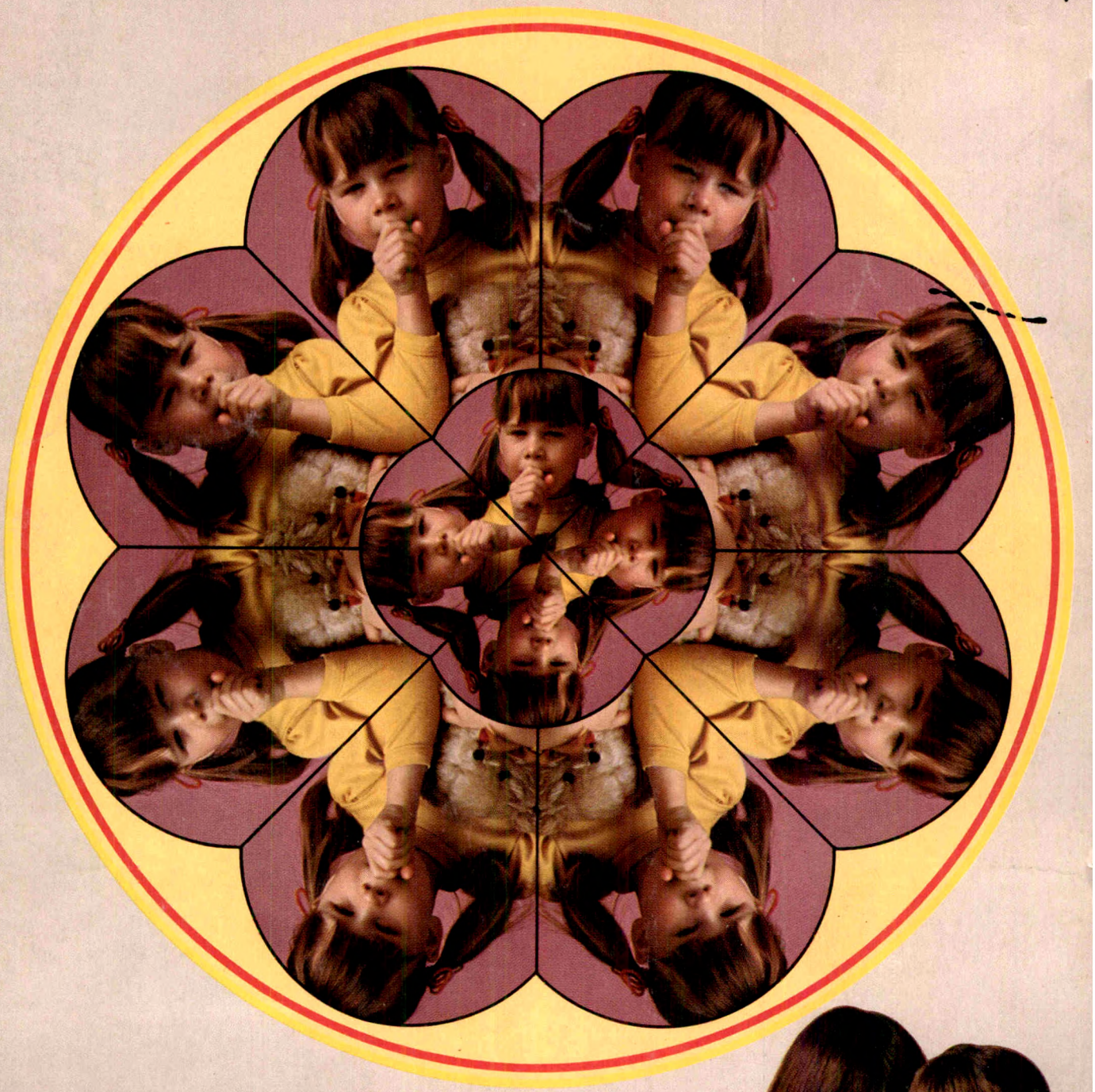

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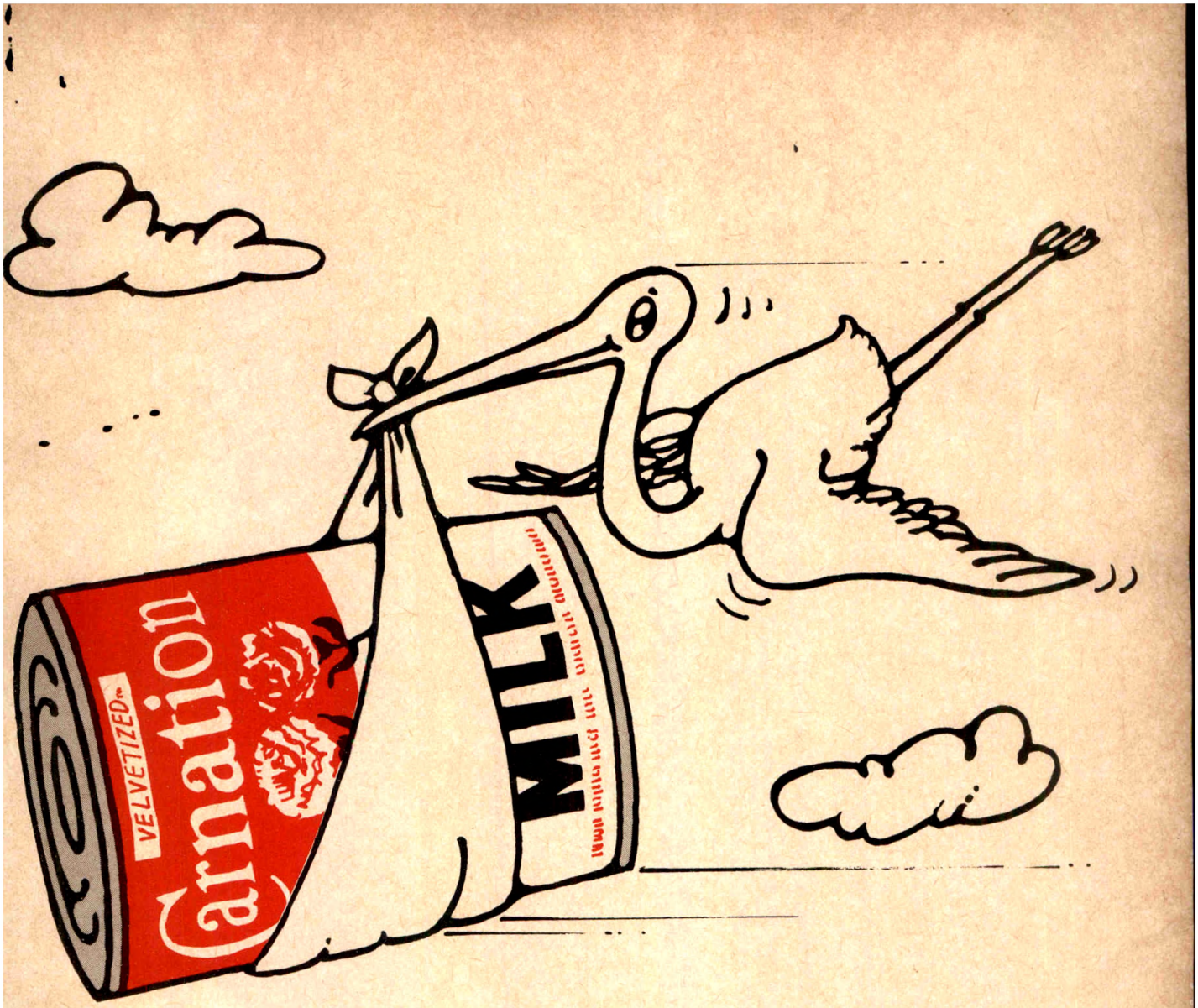

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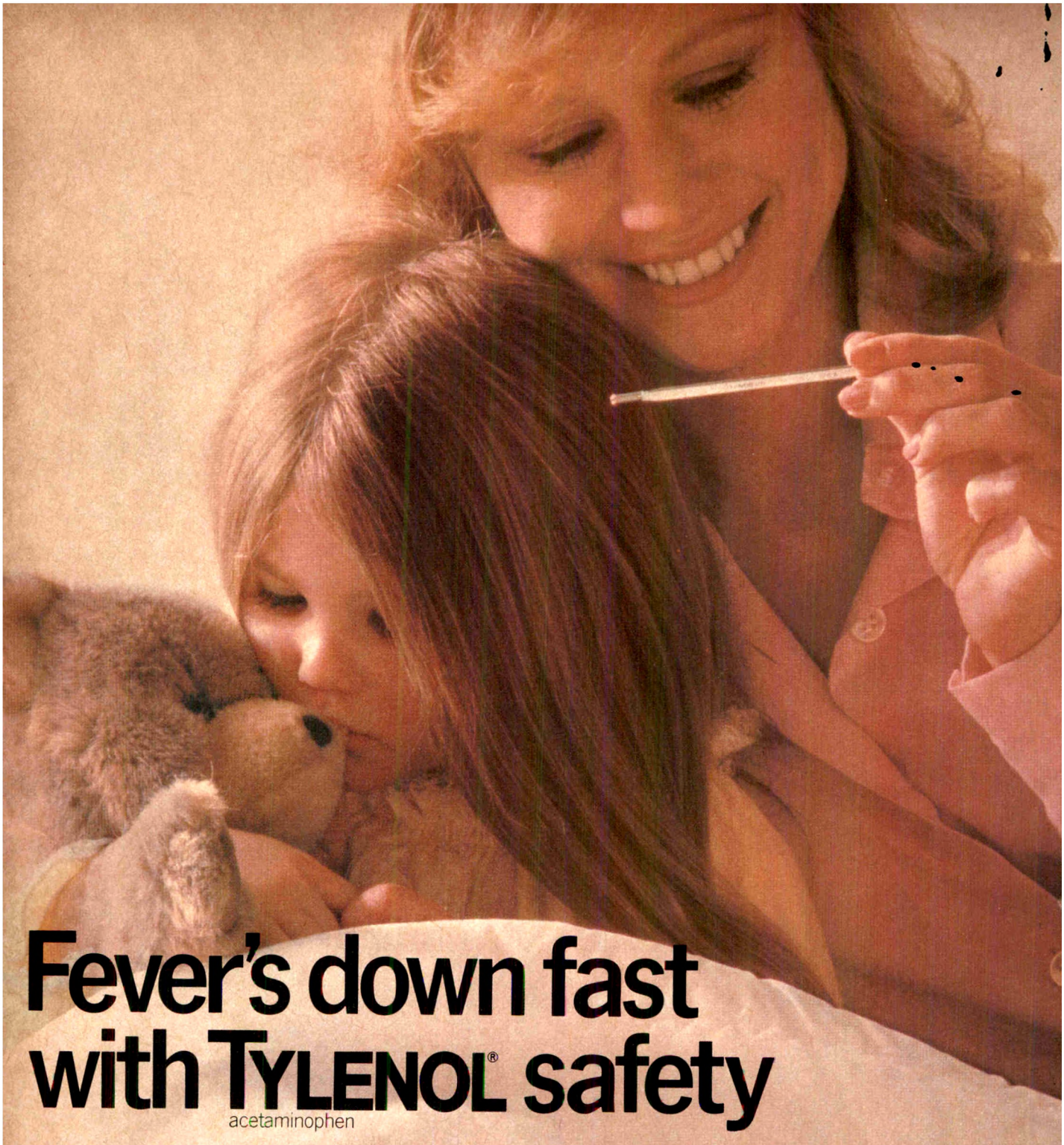

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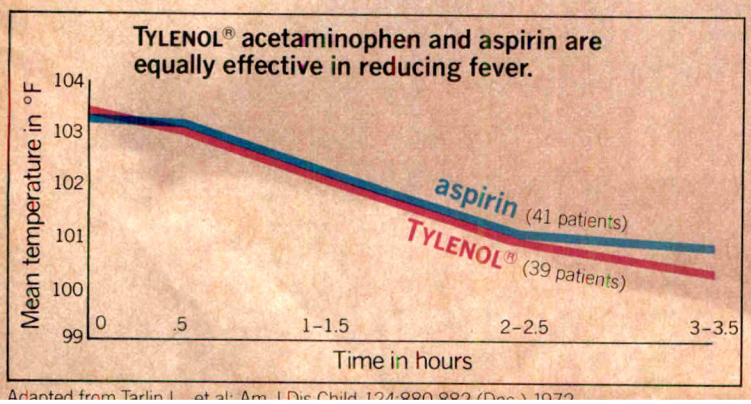

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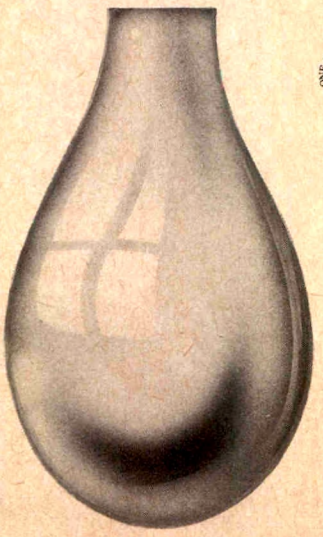

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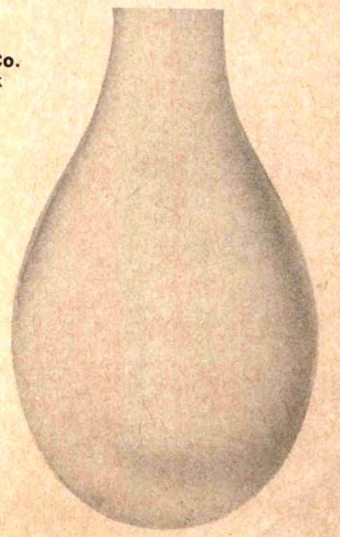

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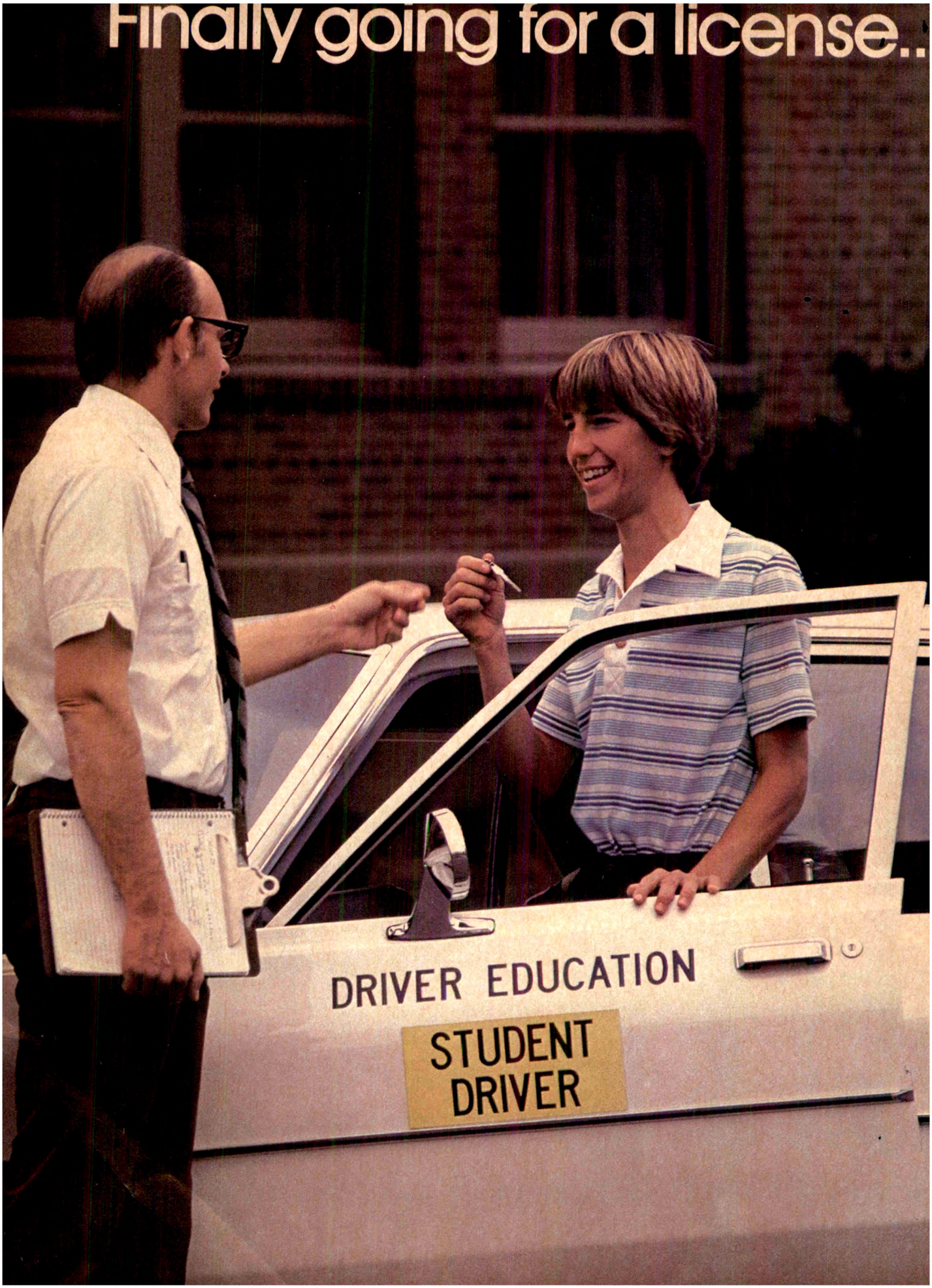
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See overleaf for brief summary of prescribing information

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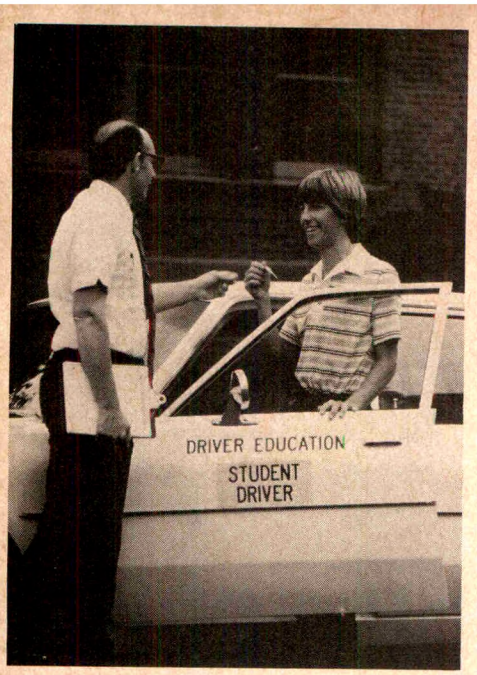


Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

A BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported but do not appear dose related. (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increased dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

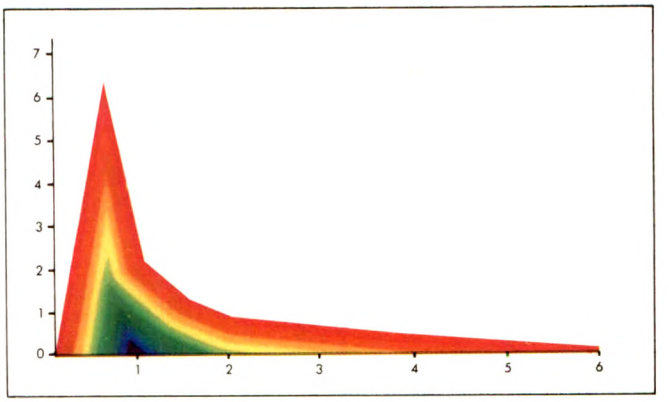
THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

0013326

ABBOTT

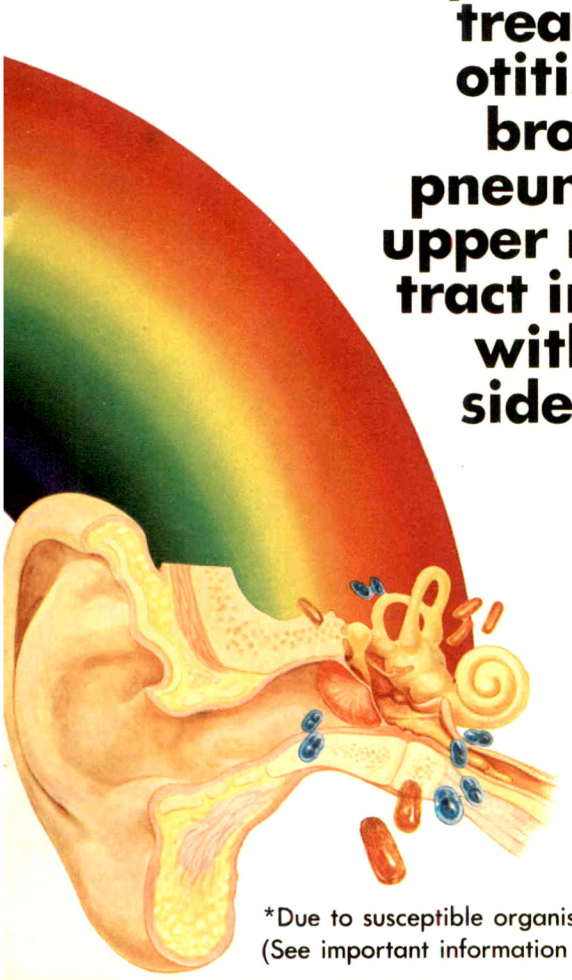
more than just spectrum

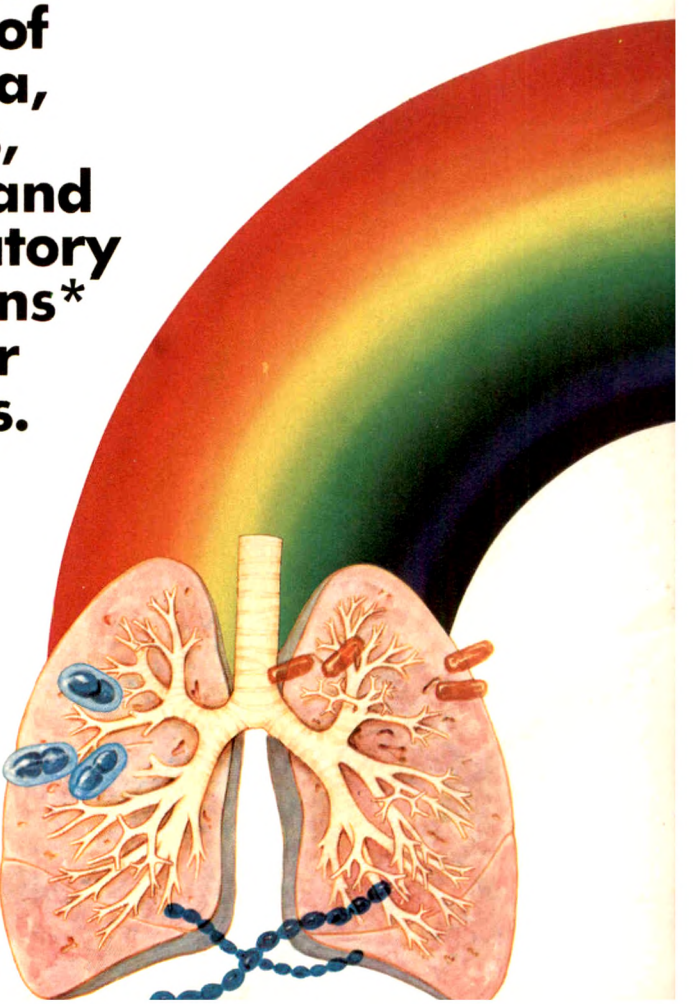


New CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Efficacy proven in the treatment of otitis media, bronchitis, pneumonia and upper respiratory tract infections* with fewer side effects.





*Due to susceptible organisms
(See important information on last page.)

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(cyclacillin) Tablets/ Suspension

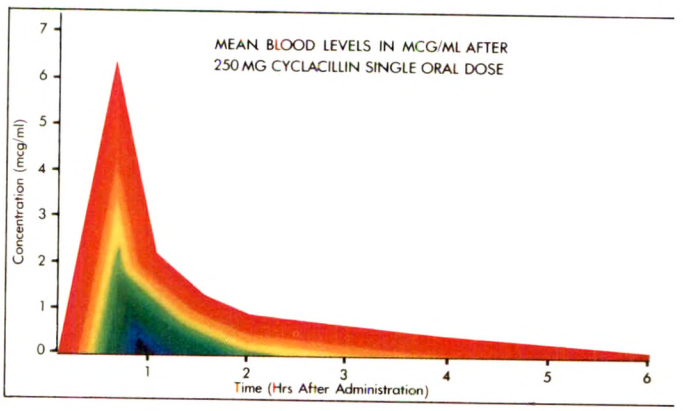
efficacy with fewer sid ampicillin confirmed i studies of 2,58

Rapid, virtually complete absorption from GI tract

Rapid onset of action—mean peak serum levels within 30 minutes

Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)

Rapidly excreted unchanged in the urine—1½ times faster than ampicillin



Clinical efficacy of CYCLAPEN® in otitis media†

Causative Organism		No. of Patient
S. pneumoniae	96	82
	95	
H. influenzae	88	96
	85	

% Clinical Response
% Bacterial Eradication

more than just spectrun in otitis media

*Includes all patients treated. 2,415 evaluated for safety; 1,819 evaluated for efficacy.

†Due to susceptible organisms.

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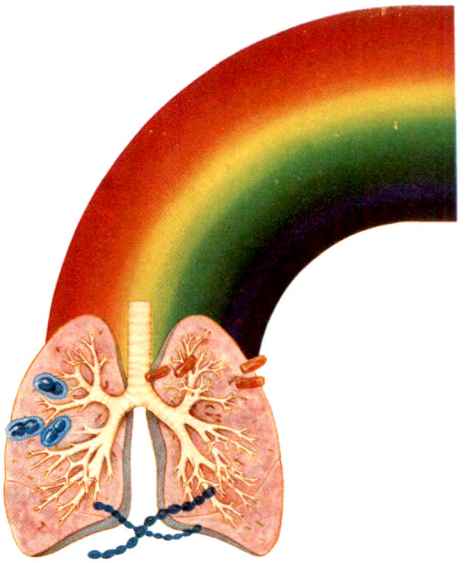
ffects than louble-blind patients*



wer side effects with CYCLAPEN® in uble-blind studies to date[1,2]

Total number of drug-related side effects in all patients	
CYCLAPEN®	128 of 1,286 (10%) of patients
ampicillin	202 of 1,129 (18%) of patients
Difference statistically significant (P <0.001)	

In bronchitis, pneumonia and upper respiratory tract infections†

High cure rate with CYCLAPEN®		
Causative Organism	Bronchitis/Pneumonia†	No. of Patients
S. pneumoniae	100 / 95	73
Chronic Bronchitis† (acute exacerbation)		
H. influenzae	92 — Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*	12
Streptococcal Sore Throat†		
Group A beta-hemolytic Streptococcus	100 / 86	44
% Clinical Response % Bacterial Eradication		

YCLAPEN® (cyclacillin) fective for otitis media† in children

Excellent clinical results in eliminating the two most common causative organisms in otitis media

Significantly lower incidence of diarrhea and skin rash in children treated with CYCLAPEN® Suspension

	diarrhea	rash
CYCLAPEN	9.1%	2.1%
ampicillin	19.2%	5.8%
	P <.0.001	P < 0.03

more than just spectrum CYCLAPEN®

(cyclacillin) Tablets/ Suspension

Gold JA, Hegarty CP, Deitch MW, Walker BR: Double-blind clinical trials of oral cyclacillin and ampicillin, *Antimicrob Ag Chemother* 15:55-58, (Jan.) 1979.

Data on file, Wyeth Laboratories.

ee important information on next page.)

Wyeth Laboratories
Philadelphia, Pa 19101

New from Wyeth Laboratories

CYCLAPEN®
(cyclacillin) Tablets/ Suspension

Usual children's dosage: 50 to 100 mg/kg/day in equally spaced doses, depending on severity.

more than just spectrum in otitis media, bronchitis, pneumonia, and upper respiratory tract infections*

- Rapid, virtually complete absorption from GI tract
- Rapid onset of action—mean peak serum levels within 30 minutes
- Exceptionally high peak blood levels—3 times greater than ampicillin (clinical efficacy may not always correlate with blood levels)
- Rapidly excreted unchanged in the urine—1½ times faster than ampicillin
- Significantly fewer episodes of diarrhea and skin rash than reported with ampicillin in studies to date
- Excellent clinical response and outstanding bacterial eradication documented in double-blind studies involving 2,581 patients
- New CYCLAPEN® Suspension—great-tasting raspberry punch flavor

*Due to susceptible organisms.

How Supplied

CYCLAPEN® (cyclacillin) tablets:
250 mg scored tablets
500 mg scored tablets

CYCLAPEN® (cyclacillin) for oral suspension
125 mg per 5 ml:
100 ml and 200 ml bottles
250 mg per 5 ml:
100 ml and 200 ml bottles

Indications

Cyclapen® (cyclacillin) has less in vitro activity than other drugs in the ampicillin class of antibiotics and its use should be confined to the indications listed below.

Cyclapen® is indicated for the treatment of the following infections:

RESPIRATORY TRACT
Tonsillitis and pharyngitis caused by Group A beta-hemolytic streptococci
Bronchitis and pneumonia caused by *S. pneumoniae* (formerly *D. pneumoniae*)
Otitis Media caused by *S. pneumoniae* (formerly *D. pneumoniae*) and *H. influenzae*
Acute exacerbation of chronic bronchitis caused by *H. influenzae**

*Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*.

SKIN AND SKIN STRUCTURES (integumentary) infections caused by Group A beta-hemolytic streptococci and staphylococci, non-penicillinase producers.

URINARY TRACT INFECTIONS caused by *E. coli* and *P. mirabilis*. (This drug should not be used in any infections caused by *E. coli* and *P. mirabilis* other than urinary tract infections.)

NOTE: Cultures and susceptibility tests should be performed initially and during treatment to monitor the effectiveness of therapy and the susceptibility of bacteria. Therapy may be instituted prior to the results of sensitivity testing.

Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to penicillins.

Warnings

CYCLACILLIN SHOULD ONLY BE PRESCRIBED FOR THE INDICATIONS LISTED IN THIS INSERT.

CYCLACILLIN HAS LESS *IN VITRO* ACTIVITY THAN OTHER DRUGS OF THE AMPICILLIN CLASS ANTIBIOTICS. HOWEVER, CLINICAL TRIALS HAVE DEMONSTRATED THAT IT IS EFFICACIOUS FOR THE RECOMMENDED INDICATIONS.

SERIOUS AND OCCASIONAL FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING PENICILLIN.

ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL ADMINISTRATION, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE ARE REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY REACTIONS WHO EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH A CEPHALOSPORIN. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE ABOUT PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY SHOULD BE INITIATED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

PREGNANCY: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to ten times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cyclacillin is administered to a nursing woman.

Adverse Reactions

The oral administration of cyclacillin is generally well tolerated.

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to **penicillins** or in those with a history of allergy, asthm fever, or urticaria.

The following adverse reactions have been reported with the use of cycla diarrhea (in approximately 1 out of 20 patients treated), nausea and vo (in approximately 1 in 50), and skin rash (in approximately 1 in 60). Is instances of headache, dizziness, abdominal pain, vaginitis, and urticari been reported. (See WARNINGS)

Other less frequent adverse reactions which may occur and that have reported during therapy with other penicillins are: anemia, thrombocyto thrombocytopenic purpura, leukopenia, neutropenia and eosinophilia. reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been repo

Dosage and Administration

INFECTION*	ADULTS	CHILDREN
		Dosage should not in a dose higher thar for adults.
Respiratory Tract		
Tonsillitis & Pharyngitis**	250 mg q.i.d. in equally spaced doses	body weight <20 k lbs) 125 mg q.i. equally spaced dose body weight >20 k lbs) 250 mg q.i. equally spaced dose
Bronchitis and Pneumonia		
Mild or Moderate Infections	250 mg q.i.d. in equally spaced doses	50 mg/kg/day q.i. equally spaced dose
Chronic Infections	500 mg q.i.d. in equally spaced doses	100 mg/kg/day q.i. equally spaced dose
Otitis Media	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/kg/d equally spaced dose pending on severity
Skin & Skin Structures	250 mg to 500 mg q.i.d. in equally spaced doses depending on severity	50 to 100 mg/kg/d equally spaced dose pending on severity
Urinary Tract	500 mg q.i.d. in equally spaced doses	100 mg/kg/day in eq spaced doses.

*As with antibiotic therapy generally, treatment should be continued minimum of 48 to 72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.

**In infections caused by Group A beta-hemolytic streptococci, a minimu 10 days of treatment is recommended to guard against the risk of rheur fever or glomerulonephritis.

In the treatment of chronic urinary tract infection, frequent bacteriologic clinical appraisal is necessary during therapy and may be required for se months afterwards.

Persistent infection may require treatment for several weeks.

Cyclacillin is not indicated in children under 2 months of age.

Patients with Renal Failure

Based on a dosage of 500 mg q.i.d., the following adjustment in do interval is recommended:

Patients with a creatinine clearance of >50 ml/min need no age interval adjustment.

Patients with a creatinine clearance of 30-50 ml/min should receiv doses every 12 hours.

Patients with a creatinine clearance of between 15-30 ml/min s receive full doses every 18 hours.

Patients with a creatinine clearance of between 10-15 ml/min s receive full doses every 24 hours.

In patients with a creatinine clearance of ≤10 ml/mi serum creatinine values of ≥ 10 mg %, serum cyclacillin levels are re mended to determine both subsequent dosage and frequency.

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Philadelphia, Pa. 19101

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Because there is no substitute for real milk.

Since the offending antigen in cow's milk is usually lactalbumin, a specific protein, Meyenberg Goat Milk has frequently proven a practical and successful substitute for cow's milk. Goat milk does not deprive the infant of the important and irreplaceable values of milk, such as occurs when synthetic milk formulas are used.

Meyenberg Goat Milk is nutritionally equal to cow's milk in protein, carbohydrate, and fat. It contains no crude fibers or other extraneous materials which cause digestive upset.

Available in Evaporated and Powdered form. Send the enclosed coupon for further information and a full-size can. Meyenberg™ BRAND

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1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 131:295-296, 1977.
2. Koller LR: *Ultraviolet Radiation*, ed 2. New York, John Wiley & Sons Inc, 1965, pp 141-160.
3. Daughaday WH: The adenohypophysis, in Williams RH (ed): *Textbook of Endocrinology*, ed 5. Philadelphia, WB Saunders Co, 1974, pp 31-79.

Do not include unpublished data, personal communications, or manuscripts "in preparation" or "submitted" in the list of references. Such material, if essential, may be incorporated in the body of the article.

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Recurrent Abdominal Pain in Childhood

Recent studies report recurrent abdominal pain in childhood as an indication for upper endoscopy. The use of this procedure or exploratory laparotomy in children with recurrent abdominal pain[1,2] has prompted the following reappraisal.

There is a confusion in the diagnosis and management of recurrent abdominal pain. Specifically, there is no clear definition of recurrent abdominal pain and there is only vague knowledge of its etiology. No diagnostic markers have been elucidated, no proved effective treatment is available, and no prospective studies of outcome have been performed.

No one has clearly defined recurrent abdominal pain. Apley[3] emphasized the presence of three discrete episodes of abdominal pain occurring over a minimum of a three-month period and interfering with the regular activities and school attendance of the child. Not addressed were considerations of the quality of the pain, duration of each episode, alleviating factors, physical condition between episodes, and absence of certain specific symptoms and signs.

Other authors[4] have applied even less stringent diagnostic criteria and have applied different terms in an attempt to explain the cause or association of the abdominal pain. Irritable colon, psychogenic abdominal pain, and allergic fatigue syndrome are some of the synonyms.[5] On the whole, they stress the vagueness of the entity and the psychological components.

Children with recurrent abdominal pain have a high frequency of behavioral and personality disorders,[3] along with some evidence of maladjustment and anxiety reactions.[6] They tend to be high-strung perfectionists and have apprehensive personalities.[3,7] Many have past histories of colic and feeding problems in infancy, and there is frequently a family history of abdominal pain among parents and relatives.[3,7] In addition, a high incidence of stressful situations within the family and at school occurs in children with recurrent abdominal pain. Despite these clinical impressions, very few studies have been conducted to establish the extent of these problems in comparison with controls. Certainly children without recurrent abdominal pain are subjected to similar stresses, and one wonders what the ultimate determinants of pain in these children are.

Various theories have been proposed to explain the pathophysiology. Abnormal pupillary dilation to stress[8] and excessive rectosigmoid spasm to neostigmine bromide[9] were described to implicate autonomic dysfunction as a possible mechanism involved in recurrent abdominal pain. It was also stated[10] that lactose malabsorption may play a part and that elimination of milk and dairy products may help. At present further work is needed in this area.

The greatest dilemma is that recurrent abdominal pain can be a symptom of both psychosomatic and organic disease. However, in a follow-up study by Stickler and Maryly[1] overt organic disease had developed in only three of 161 patients (2%) over a six- to seven-year period. Weight loss or anemia were noted retrospectively in two of three children with suspected inflammatory bowel disease. Therefore, we suggest that those children with recurrent abdominal pains have a thorough history and physical examination. Those who have no additional symptoms to suggest organic disease, no tenderness, and no pain interfering with sleep or pleasurable activities should have a minimum of diagnostic tests. Loss of weight and anemia can be signs of organic disease.[1] Several follow-up visits are needed for the pediatrician to become familiar with the patient, parents, and the environmental situation of the child. Tests performed may include urinalysis, urine culture, hemoglobin count, WBC count, ESR, and stool examination for occult blood. However, at times the parents and consequently the physician may become enmeshed in a seemingly never-ending effort to find a physical cause for the symptoms.[11] The long list of diagnostic efforts include electroencephalography, gastrointestinal barium studies, intravenous pyelograms, computerized tomographic scans, echograms, cholecystography, endoscopy, and proctoscopy. Most disturbing are the instances of exploratory laparotomies performed to rule out a possible organic disease.[1,2]

Our experience suggests that attempts at treatment with placebos are not to be recommended. Antispasmotics and sedatives may contribute to the anxiety and confuse the picture. Reassurance of the patient and family that organic disease is not the cause of recurrent abdominal pain is most helpful and in certain instances, is all that need be done. Explanation that the pain is in fact real and not imagined and that it is a normal psychosomatic reaction to stress is usually accepted. It is most helpful to be positive, reassuring, and understanding. We persuade the parents that immediate return to school is mandatory.

In the more refractory and long-standing cases, parental acceptance of a nonorganic functional etiology will be difficult unless the child is hospitalized and many of the aforementioned tests are performed. When the family accepts the idea that this disorder has no organic cause, the physician may

attempt to find and alleviate the cause of the stress. This will take time, concerned interest, and emotional support. Elective referral to psychosocial professionals may be necessary. It is important to emphasize that if the situation is not properly handled, an endless number of diagnostic tests may be performed, or the phenomenon of "physician shopping" may needlessly occur. It is this phenomenon that many times leads to extensive, often unnecessary evaluations, and to exploratory laparotomy. The pediatrician has the main responsibility of assuring the family of the benign course of the entity and preventing deplorable practices, such as exploratory laparotomy.

In conclusion, there is a need for a clear definition of recurrent abdominal pain, indications for diagnostic evaluation, and instruction in approach and treatment. Long-term controlled studies regarding the outcome of the disease, with and without intervention, are necessary for better understanding and management.

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Buffalo, NY 14222

References

1. Stickler G, Maryly DB: Recurrent abdominal pain. *Am J Dis Child* 133:486-489, 1979.
2. Johnson LF, Vanderhoof JA, Black S: The role of exploratory laparotomy for chronic abdominal pain in children. *Nebr Med J* 59:430-433, 1974.
3. Apley J: *The Child With Abdominal Pains.* London, Blackwell Scientific Publications, 1975.
4. Oster J: Recurrent abdominal pain, headache and limb pains in children and adolescents. *Pediatrics* 50:429-436, 1972.
5. Rang EH, Fairbairn AS, Acheson ED: An enquiry into the incidence and prognosis of undiagnosed abdominal pain treated in the hospital. *Br J Prev Soc Med* 24:47-51, 1970.
6. Heinild S, Malver E, Reolsgaard G: A psychosomatic approach to recurrent abdominal pain in childhood with particular reference to the x-ray appearances of the stomach. *Acta Pediatr* 48:361-370, 1959.
7. Liebman W: Recurrent abdominal pain in children. *Clin Pediatr* 17:149-153, 1978.
8. Rubin LS, Barbero GJ, Siblinga MS: Pupillary reactivity in children with recurrent abdominal pain. *Psychosom Med* 29:111-120, 1967.
9. Kopel FB, Kim IC, Barbero GJ: Comparison of rectosigmoid motility in normal children, children with RAP, and children with ulcerative colitis. *Pediatrics* 39:539-545, 1967.
10. Barr RG, Levine MD, Watkins JB: Recurrent abdominal pain of childhood due to lactose intolerance. *N Engl J Med* 300:1449-1452, 1979.
11. Weiss E: Psychogenic rheumatism. *Ann Intern Med* 26:890-900, 1947.

The Alternative Birthing Center

One Family's Experience

I have been editing copy for the JOURNAL for more than a year. In that time, I've edited case reports, poems, letters, book reviews, and editorials, by dozens of authors, practically all of them with one theme: wonder before the human body and the countless ways that it can malfunction. This, of course, reflects medicine's preoccupation with sickness. However, a recent event reminded me that a physician can be concerned with the preservation of health as well as with curing sickness, to help the patient through a difficult period with grace. This event was the birth of my daughter last April in an "alternative birthing center" in Chicago.

When my wife, Anne Ryan, learned in September 1978 that she was pregnant, she had already investigated the subject of childbirth both as it takes place in the hospital and the alternatives to hospital birth. One of my nieces had been delivered at home by an obstetrician and, as we discovered, few of the popular books on the subject had anything good to say about a hospital delivery. The complaints against hospital delivery are well known, but for us they were new and frightening. Separation of husband from wife and parent from child, the liberal use of powerful drugs, routine cutting, the high incidence of cesarean sections, all seemed to us to indicate a lack of consideration toward parent and child.

On the other hand, a home delivery was not practical. Aside from the fact that getting medical assistance would be nearly impossible, having a first child at home seemed just too risky. Then we saw an article in a local newspaper about the Alternative Birthing Center (ABC) at Illinois Masonic Hospital, Chicago. The idea behind the ABC is to simulate the conditions of a home birth as much as possible, while having modern hospital equipment and trained personnel just steps away should anything go wrong. Each delivery takes place in a large "bedroom," with ordinary table, chairs, carpeting, record player, beanbag chair, bentwood rocker, and a king-sized bed. The father or a friend

of the mother assists at the birth, and other people can witness it. The baby is not taken away after birth, and, as much as possible, the wishes of the parents are respected with regard to the medical procedures performed.

Like most good things, however, the ABC has a catch: it only accepts mothers whose deliveries will be uncomplicated. That means no breech deliveries, no multiple births, no premature children, no children more than three weeks overdue, no prolonged labors, and no mothers who have already had a cesarean section. About one mother in four who begins labor in the ABC "washes out," and is transferred to the regular labor and delivery area. The thought that we might still wind up in a regular labor and delivery facility was disturbing, but we decided the reward was worth the risk, and so signed up and began our preparations.

First, we attended hospital prenatal classes, which taught about nutrition, exercise, labor, etc, and included a tour of the labor and delivery area. It was interesting to compare reactions to the cozy atmosphere of the ABC and the impersonal atmosphere of the regular labor and delivery area. The delivery room itself, with its cold tile walls and utilitarian delivery table, well-worn restraining straps hanging from its sides, was enough to convince several couples to inquire about the ABC.

Late in February we began Lamaze training with a group in the home of a registered nurse. The six weekly sessions covered standard Lamaze material: instruction in anatomy and recognition of the various stages of labor; breathing exercises with which to cope with labor; conversation with other young parents on what to expect; and practice in dealing with various aspects of labor. By the end of the six weeks, we felt we were ready.

Naturally, labor did not go according to the standard scenario. We were awakened by Anne's contractions at about 1 AM, strong contractions coming about every three minutes and lasting 90 to 110 s. After a few minutes of this, it was obvious that the labor had skipped the first stage and gone directly into transition-stage. While I made the phone calls, Anne was able to cope with the contractions with her breathing exercises; a friend then drove us to the hospital. To my mind, this is the most important lesson of our experience: if we had decided to have a traditional delivery, with everything left in the hands of the physician, we would not have been ready for a labor that came on that quickly and that hard. Without Lamaze training, we may well have panicked and turned a serious but manageable situation into a dangerous one.

By 2:30 AM we were at the hospital. Anne had already dilated to 9 cm and, naturally, was very irritable and in great discomfort. It is difficult to collect my thoughts about what happened during the next 2½ hours before the baby was born, mostly because I was very busy helping with the labor: helping Anne regulate her breathing, encouraging her ("verbal anesthesia," the Lamaze people call it), and helping her to a comfortable position. (Toward the end, she was most comfortable sitting on the bed with the beanbag chair supporting her back; she even delivered in that position.) My recollection is that time was somehow compressed, hours passing like minutes; also, I "remember" some things that could not possibly have happened; for example Anne wearing her street clothes during labor, when I know she must have been wearing a hospital gown.

The nurse-clinician helped us in many small ways. The obstetrician, Leticia Dacanay, MD, arrived around 3:00 AM, and after what seemed to be a short time Anne began to push. Spontaneously, we fell into a position in which she would hold my hands and pull while pushing; I would pull back and give her something to brace herself against. I could see a large lump descending, and finally a small tuft of hair appeared. Dr Dacanay laid out a pair of surgical gloves in case I wanted to catch the baby, but I was too busy helping Anne push to put them on.

A cut was needed. There was a great rush of fluid, then the baby's head appeared. I looked down at it, watched it slowly rotate; it seemed as if the infant was looking around at the world. Then one more push, and at 3:56 AM our daughter Marian skidded out onto the mattress. She was bluish at first, but pinked up nicely within a few minutes (Apgar scores of 6 and 9 at 1 and 5 minutes of life, if you're interested); quickly, Dr Dacanay and the nurse had her cord clamped and cut, her throat cleared, and the silver nitrate into her eyes.

And what seemed like a split second later (although it was at least ten minutes), I was picking her up. She seemed to be squinting, so I maneuvered her face into my shadow and her eyes jumped open. Then I gave her to Anne, who suckled her. Marian spent the day with us, and we took her home later that afternoon.

It is tempting to fashion a rule from all this; however, Marian's birth may not have been typical. The alternative birthing movement is a large one; it contains a few people who are irrationally hostile to physicians and modern medicine, and a few who insist on demonstrating once more that a little knowledge is a dangerous thing. However, some lessons can be learned from our experience, small points that, to a patient, seem to be forgotten in the daily hustle of medical care. First, an informed patient is better off than an ignorant one. Second, a patient who manages his own health as far as prudence allows will be better off than one whose health is managed for him. Third, a patient who is reasoned with will be more cooperative than one who is ordered around. Finally, patient involvement is economical: Illinois Masonic, for example, charges for the ABC about one third of what it charges for the regular labor and delivery area.

The birth of our daughter was one of the great experiences of our lives. It happened this way thanks largely to medical personnel who cared. I only hope that the alternative birthing movement's spirit of cooperation between patient and physician can be applied to every branch of American medicine.

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RA27/3 Rubella Vaccine

A Four-Year Follow-up

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• **RA27/3 rubella vaccine was given to 418 subjects aged 1 to 17 years in 1974, 201 of whom participated in a four-year follow-up study. Two vaccine-associated complications were reported. A 5-year-old boy had transient arthritis of the hip, and a 1-year-old boy had a pigmented macule at the inoculation site. Rubella reinfection was uncommon, occurring at most in three of our subjects. All of the 186 susceptible children seroconverted, and 182 had hemagglutination-inhibiting (HI) titers of 8 or greater at four-year follow-up (geometric mean titer, 30.3). In the four children whose HI titers declined to undetectable levels, both HI and neutralizing (Nt) antibodies had developed immediately postimmunization, and two had Nt titers at follow-up despite loss of HI antibodies. RA27/3 vaccine boosted HI titers in 15 seropositive subjects, but titers returned to preimmunization levels four years later. We concluded that RA27/3 vaccine produced durable immunity with very low rates of rubella reinfection and secondary vaccine failure during the four years since immunization.**

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RA27/3 is the only rubella vaccine presently licensed and available in the United States. Since RA27/3 is now a part of routine pediatric immunizations in our country, it is important to document its long-term effectiveness in children. We immunized 418 children from Minnesota and Wisconsin with RA27/3 rubella vaccine in 1974.[1] A follow-up study was conducted in 1978, at which time we obtained histories of vaccine reactions and rubella-like illnesses and measured rubella serum antibody titers. We were especially interested in the percent of children with persistent rubella hemagglutination-inhibiting (HI) antibodies, because a 1977 investigation in suburban Minneapolis indicated that 58 (36%) of 159 children vaccinated with HPV77 DE5 strain rubella vaccine lacked HI titers when tested four years after immunization.[2]

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SUBJECTS AND METHODS

The subjects had been vaccinated subcutaneously during a field study of RA27/3 vaccine in 1974.[1] All who had been seronegative and some of those who had been seropositive prior to immunization were invited to participate. A history of postimmunization reactions, exposure to rubella, illness resembling rubella, and rubella revaccination was taken from the subjects or their parents.

Venous blood was collected and tested for rubella HI antibodies as previously described.[2,3] The follow-up serum sample (S_3) was analyzed simultaneously with the preimmunization (S_1) and postimmunization (S_2) samples from the same subject. The S_1 and S_2 sera collected in 1974 had been stored since then at −70 °C. Plaque-reducing neutralizing (Nt) antibody titers were performed in RK-13 cells according to a modification of the method of Fogel and Plotkin.[4] The HI and Nt titers are expressed as reciprocals of serum dilutions. This study was approved by the University of Minnesota Committee on the Use of Human Subjects in Research, and informed consent was obtained from the children or their parents before enrollment.

RESULTS

A total of 201 vaccinees participated in the four-year follow-up study. Their ages at the time of vaccination ranged from 1 to 17 years (median, 4.0 years; mean, 4.1 years). The median follow-up period was 4.1 years (mean, 4.2 years; range, 3.6 to 4.9 years), during which time none of the subjects had been revaccinated. The median age at the time of follow-up testing was 8.0 years (mean, 8.3 years; range, 4.9 to 20.9 years).

Two complications associated with vaccination were reported at the time of follow-up examination. In a 5-year-old boy who was seronegative prior to vaccination, arthritis of the left hip developed 31 days postimmunization. At the time of follow-up, his mother reported that he still experienced transient arthralgia, particularly on damp days, but his school attendance and physical activities were unimpaired. His hips were entirely normal on physical examination. In a boy who was 1 year of age and initially seronegative, a 1-cm macule developed at the vaccination site. The macule was first observed two weeks after vaccination and was still present four years later.

Only three of our vaccinees had any evidence of rubella reinfection during the follow-up period. Two girls who were seronegative and a boy who was seropositive before vaccination had fourfold or greater rises in HI titer between postimmunization (S_2 and S_3) samples. None of the three had a clinical illness that resembled rubella. The yearly incidence of rubella in Minnesota was relatively low during the period of follow-up. An average of

49 cases per year were reported to the Minnesota Department of Health between 1974 and 1978, with the fewest (18) observed in 1974 and the most (128) in 1978.

Of the 201 subjects studied, 186 had been seronegative and 15 had been seropositive before immunization (Table 1). In all of the seronegative subjects, rubella HI titers developed shortly after immunization, and thus there were no primary vaccine failures among this group. In the seropositive vaccinees, increased HI titers developed shortly after immunization, but these decreased to preimmunization levels when measured four years later. The geometric mean titers (GMTs) are displayed in Fig 1, which contrasts the effect of vaccinating seronegative and seropositive children. The rubella HI antibody responses for both groups were strikingly similar. Since there were only two postimmunization GMT values for each group, antibody titers seemed to decline steadily with time. Because that may not have been precisely the case, titers from seronegative subjects whose S_2 samples were collected 4, 8, 10, 12, or 14 weeks postvaccination were plotted separately (Fig 2). The points then represent different subjects, but the curve that connects them probably more accurately reflects the actual titer changes. The HI titers peaked eight to 12 weeks after immunization, had a somewhat rapid rate of decline shortly thereafter, and then leveled off (Fig 2). Children who were seronegative before vaccination had a GMT of 30.3, an arithmetic mean titer of 38.7, and a modal HI titer of 32 four years postimmunization.

Four (2.2%) of the 186 children who seroconverted after immunization had HI titers decline to less than 8 at the four-year examination (Table 2). These children would be considered secondary vaccine failures by HI testing. Plaque-reducing Nt titers were performed in addition to HI tests to characterize further their immune responses. In all four, HI and Nt titers developed immediately postimmunization. After four years, two subjects still had Nt antibodies, although HI titers had declined to undetectable levels.

Eleven vaccinees had HI titers of 8 at follow-up examination. Their sera also were tested for plaque-reducing Nt antibodies, and all had titers of 8 or greater. We could not evaluate the effect of passively transferred maternal antibody on durability of immuni-

Table 1.—Rubella Hemagglutination-Inhibiting (HI) Antibody Titers After RA27/3 Rubella Vaccine

Preimmunization Status*	Subjects Tested	Geometric Mean Titers			Postimmunization Titers < 8	
		S_1†	S_2‡	S_3§	S_2	S_3
Seronegative	186	0.0	74.0	30.3	0	4(2.2%)
Seropositive	15	36.8	84.4	35.1	0	0

*Seronegative indicates HI titer less than 8; seropositive, HI titer 8 or greater.
†S_1 indicates sera collected preimmunization.
‡S_2 indicates sera collected from 24 to 255 days postimmunization (median, 53 days).
§S_3 indicates sera collected from 3.6 to 4.9 years postimmunization (median, 4.1 years).

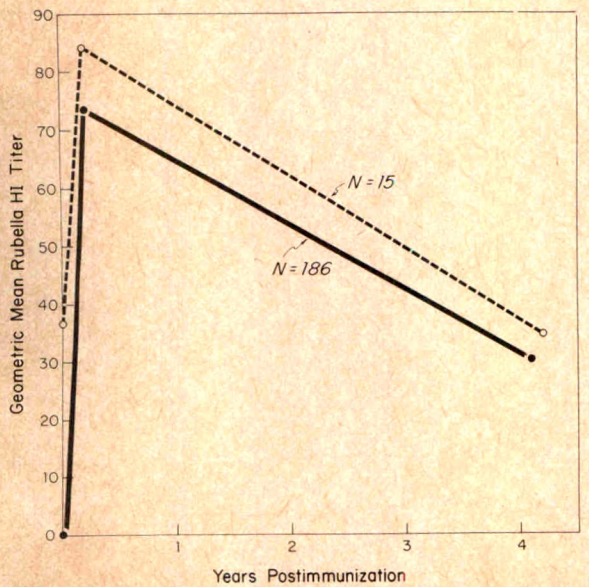

Fig 1.—Geometric mean rubella HI titers after RA27/3 immunization. Solid line shows results for 186 subjects seronegative before immunization. Dotted line represents 15 subjects seropositive before immunization.

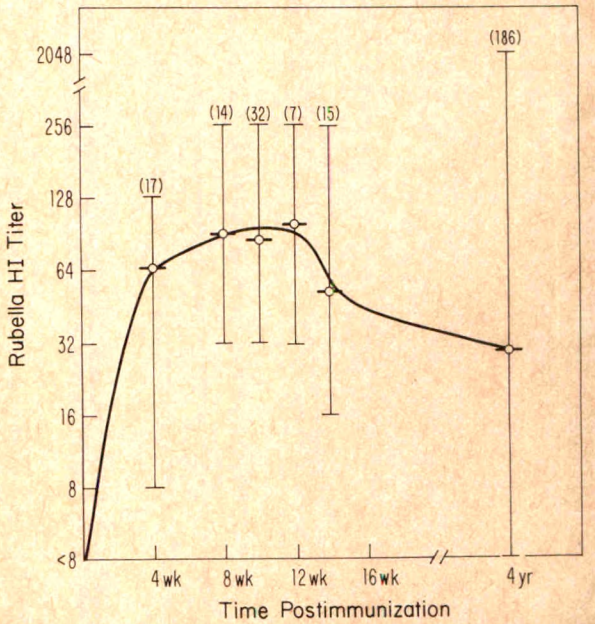

Fig 2.—Rubella HI titers induced by RA27/3 vaccine in children initially seronegative. Number of subjects at each time tested after immunization is given in parentheses. Ranges in HI titer for each point are indicated by horizontal lines. Curve is estimated by connecting geometric mean titers (indicated by circles).

Table 2.—Rubella Hemagglutination-Inhibiting (HI) and Neutralizing (Nt) Antibodies in RA27/3 Vaccinees Whose HI Titers Declined to Less Than 8 After Four Years

Sex	Age at Vaccination, yr/mo	S_1* Titers		S_2† Titers		S_3‡ Titers	
		HI	Nt	HI	Nt	HI	Nt
M	10/7	< 8	< 2	32	512	< 8	16
F	3/10	< 8	< 2	64	256	< 8	4
M	1/1	< 8	< 2	64	256	< 8	< 2
M	11/1	< 8	< 2	128	1,024	< 8	< 2

*S_1 indicates preimmunization sera.
†S_2 indicates sera collected 29 to 58 days (mean, 45 days) postimmunization.
‡S_3 indicates sera collected four years postimmunization.

ty after RA27/3 vaccination, because only eight children were immunized when 13 months of age or younger.

COMMENT

RA27/3 rubella vaccine induced durable immunity in the children studied with no primary vaccine failures, little evidence of reinfection, and a very low rate of secondary vaccine failure. At most, two (1.1%) of 186 initially seronegative vaccinees and one (6.7%) of 15 initially seropositive subjects had rubella reinfection during the four years postimmunization. Only four (2.2%) of 186 initially seronegative subjects demonstrated secondary serologic failure by HI testing, and two (1.1%) by Nt testing.

The reason for the loss of HI titers in four of our subjects is not readily apparent. Horstmann published data suggesting that children who mounted feeble HI responses to HPV77 DE5 rubella vaccine were most likely to lack HI titers at follow-up testing.[5] This was not true for our children who lost HI antibody, since they initially responded to RA27/3 vaccination with relatively high HI and Nt titers. Another possible reason for serologic failure is the age at immunization. Recently gathered data suggest that passively transferred maternal antibody may interfere with persistence of measles[2,6] and rubella[2] HI titers. However, passively transferred maternal antibody can be implicated in only one of our four vaccinees whose titer declined to an undetectable level, since the other three had been immunized when much older than 15 months. The vaccine could not have been inactivated by improper manufacture, transportation, or storage since it induced HI and Nt antibody titers shortly after immunization. Host immunologic responses, possibly genetically modulated, may be the reason for loss of titer with time in a few subjects. This possibility is intriguing, since histocompatibility antigens have been associated with susceptibility to rubella infection and rates of seropositivity in normal adult populations.[7] Fortunately, the present period of follow-up observation, as well as other studies, indicate that primary and secondary RA27/3 failures are uncommon. The overall RA27/3 serologic failure rate has been reported to be between 0% and 2.6%.[8-12]

The critical question not yet resolved is: do children, especially girls, who have no measurable antibody titer at follow-up testing need revaccination? RA27/3 vaccine can boost rubella HI titers. Fourfold or greater HI titer increases were found in 28 (23%) of 122 children who were seropositive before immunization in our 1974 RA27/3 field trial.[1] Since children with a history of rubella immunization were excluded from that study, those seropositive before immunization had antibody induced by natural infection. If RA27/3 vaccine can boost natural immunity, it should be able to boost vaccine-induced immunity as well. We have found in a preliminary study that RA27/3 vaccine given subcutaneously boosted HI titers in all ten children whose HI and Nt titers were undetectable four years after immunization with HPV77 DE5 rubella vaccine. Brandling-Bennett et al[13] have also demonstrated a booster effect of RA27/3 given either subcutaneously or intranasally. However, it is not clear that a booster immunization is needed because the level of antibody necessary to prevent rubella infection with viremia is not known. In the ten children whom we revaccinated, viremia could not be detected, but the number of samples and size of the group were small. Clearly, additional revaccination and challenge studies are needed to define the risk, if any, of wild rubella virus to a seronegative vaccinee. At present, it is reassuring that congenital rubella has not been reported in a term baby born to a woman appropriately vaccinated prior to pregnancy.

To our knowledge, the few follow-up reports available indicate that RA27/3 vaccine provides long-term immunity in children. Hillary and Freestone[8] demonstrated durable immunity for at least six years in 16 British children vaccinated between the ages of 15 months and 8 years. Buser[9] found that HI antibody titers persisted at least seven years in 15 Swiss children. Zourbas et al[14] found that HI titers were quite stable, persisting for at least five years in girls from Brittany who had been immunized at 11 to 13 years of age.

Rubella reinfections after RA27/3 immunization are uncommon. MacDonald et al[12] conducted a study six to eight years after immunization of women with RA27/3 vaccine or Cendehill vaccine. Reinfections were documented in only two of 196 women who received RA27/3 vaccine either subcutaneously or intranasally. In contrast, 14 (25.5%) of 55 women who had been given Cendehill vaccine had evidence of reinfection. Rubella reinfections, as indicated by fourfold or greater rises in titer between postimmunization samples, did not occur in the reports by Hillary and Freestone[8] or Buser.[9] Zourbas et al[10] did find evidence of reinfection after administration of RA27/3 vaccine, but the rate was not given. The reinfection rate in the present study was at most 1.5% (3/201). It might be as low as zero, because fourfold titer rises between postimmunization sera conceivably could be the result of delayed development of peak vaccine-induced titers. Since rubella infections, as reflected by cases reported to the Minnesota Department of Health, were not common during the follow-up peri-

od, the low rate of reinfection could be due to lack of exposure. Nevertheless, our findings combined with the other cited studies suggest that rubella reinfections are unusual in RA27/3 vaccinees.

Rubella reinfection certainly is undesirable if accompanied by viremia. However, subclinical wild rubella infection could be beneficial as a natural booster of immunity and may be responsible for persistence of rubella antibody titers in some vaccinees.

Three years after HPV77 DE5 immunization, Schluederberg et al found that Nt titers done in Vero cells were absent in three (21%) of 14 vaccinees with HI titers of 8 and in two of 14 with titers of 16.[15] Because of this finding and the possibility that Nt antibodies may correlate better with resistance to rubella reinfection than HI antibodies, we tested sera from all 11 vaccinees who had follow-up HI titers of 8. These 11 subjects had Nt titers of 8 or greater by a plaque-reducing method in RK-13 cell cultures. Thus, our subjects with low HI antibody titers did not lack Nt antibody. In fact, two of four children who lost HI antibody four years after RA27/3 had detectable Nt antibody.

Serologic failures in the present study were much less frequent than those found after HPV77 DE5 vaccination in a suburban Minneapolis pediatric practice (2.2% vs 36%).[2] The design of the HPV77 DE5 study, however, was different than the RA27/3 follow-up. RA27/3 vaccine had been administered in a field trial and was not given as a part of routine pediatric immunization. Second, sera from the HPV77 DE5 vaccinees were not collected in the immediate postimmunization period and thus we could not determine whether serologic failure was primary or secondary. Our data suggest that in HPV77 DE5 failures, antibody response either never developed or was very transient. A third difference was that only eight (4%) of 186 initially seronegative children were vaccinated with RA27/3 when younger than 14 months of age, whereas 80 (50%) of 159 were vaccinated with HPV77 DE5 when younger than 14 months old. The study of HPV77 DE5 vaccinees showed that age at time of immunization was important. Children vaccinated at 13 months of age or younger had a significantly higher serologic failure rate than those vaccinated at 14 months or older ($P < .005$). The high proportion of serologic failures after HPV77 DE5 therefore could be due in part to passive maternal antibody blunting the active immune response. Even taking into account these obvious differences, however, the conclusion that RA27/3 vaccine provided longer lasting serologic immunity than HPV77 DE5 seems justified.

Besides durable immunity, there are other advantages of RA27/3 vaccine. RA27/3 virus is grown in WI-38 human diploid fibroblast cells that have been exhaustively studied and seem to be free of infectious or oncogenic agents.[16] Also, qualitative and quantitative antibody responses induced by RA27/3 vaccine more closely resemble natural rubella than do those elicited by either Cendehill or HPV77 DE5 vaccines.[12,15,17]

Concern has been raised about risk to the fetus associated with RA27/3 vaccine.[18] However, there is evidence to support its lack of teratogenicity.[19] Since rubella immunization efforts are being aimed not only at preschool children, but at young women as well, and since RA27/3 is the only rubella vaccine now available in our country, much more information should be available shortly.

All things considered, we are fortunate that RA27/3 vaccine is now licensed and distributed in the United States. Available data indicate that it is safe and will provide both short- and long-term protection against rubella. Nevertheless, follow-up studies must continue, since vaccination of a 15-month-old girl requires at least 40 years of immunity to assure that none of her offspring will have congenital rubella.

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References

1. Balfour HH Jr, Balfour CL, Edelman CK, et al: Evaluation of Wistar RA27/3 rubella virus vaccine in children. *Am J Dis Child* 130:1089-1091, 1976.

2. Balfour HH Jr, Amren DP: Rubella, measles, and mumps antibodies following vaccination of children: A potential rubella problem. *Am J Dis Child* 132:573-577, 1978.

3. Palmer DF, Cavallaro JJ, Herrmann KL: A procedural guide to the performance of rubella hemagglutination-inhibition tests. Atlanta, Center for Disease Control Immunology Series No. 2, revised, August 1977.

4. Fogel A, Plotkin SA: Markers of rubella virus strains in RK_{13} cell culture. *J Virol* 3:157-163, 1969.

5. Horstmann DM: Controlling rubella: Problems and perspectives. *Ann Intern Med* 83:412-417, 1975.

6. Yeager AS, Davis JH, Ross LA, et al: Measles immunization: Successes and failures. *JAMA* 237:347-351, 1977.

7. Honeyman MC, Dorman DC, Menser MA, et al: HLA antigens in congenital rubella and the role of antigens 1 and 8 in the epidemiology of natural rubella. *Tissue Antigens* 5:12-18, 1975.

8. Hillary IB, Freestone DS: Persistence of antibody induced by rubella vaccine (Wistar RA27/3 strain) after six years. *J Hyg* 75:407-411, 1975.

9. Buser F: Rötelnprobleme in der Praxis des rubeolengeschädigte Kind. *Praxis* 64:88-93, 1975.

10. Zourbas J, Senecal J, Morvan A, et al: Seró-épidémiologie rubéoleuse pré- et post-vaccinale en Bretagne (1971-1975): Étude comparative des souches Cendehill et Plotkin. *Ann Pédiat* 23:111-118, 1976.

11. Black FL, Lamm SH, Emmons JE, et al: Durability of antibody titers induced by RA27/3 rubella virus vaccine. *J Infect Dis* 137:322-323, 1978.

12. MacDonald H, Tobin JO'H, Cradock-Watson JE, et al: Antibody titres in women six to eight years after the administration of RA27/3 and Cendehill rubella vaccines. *J Hyg* 80:337-347, 1978.

13. Brandling-Bennett AD, Jackson RS, Halstead SB, et al: Serologic response to revaccination with two rubella vaccines. *Am J Dis Child* 130:1081-1084, 1976.

14. Zourbas J, Senecal J, Roussey A, et al: L'immunité rubéolique 5 ans après la vaccination. *Nouv Presse Med* 7:1297, 1978.

15. Schluederberg A, Horstmann DM, Andiman WA, et al: Neutralizing and hemagglutination-inhibiting antibodies to rubella virus as indicators of protective immunity in vaccinees and naturally immune individuals. *J Infect Dis* 138:877-883, 1978.

16. Plotkin SA, Farquhar J, Katz M, et al: A new attenuated rubella virus grown in human fibroblasts: Evidence for reduced nasopharyngeal excretion. *Am J Epidemiol* 86:468-477, 1967.

17. Plotkin SA, Farquhar JD, Ogra PL: Immunologic properties of RA27/3 rubella virus vaccine: A comparison with strains presently licensed in the United States. *JAMA* 225:585-590, 1973.

18. Goldwater PN, Quiney JR, Banatvala JE: Maternal rubella at St Thomas' Hospital: Is there a need to change British vaccination policy? *Lancet* 2:1298-1300, 1978.

19. Plotkin SA: Rubella vaccination. *Lancet* 1:382, 1979.

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Fulminant Neonatal Meningococcemia

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• ***Neisseria meningitidis*** **is a rare cause of infection in infants younger than 2 months of age, presumably because of transplacental passage of protective maternal antibodies. In most reported cases of meningococcal disease in neonates, a relatively mild clinical course has been observed. A 25-day-old infant survived acute, severe meningococcemia due to group B *N meningitidis*. This organism should be considered when neonates have signs of septicemia, especially in the presence of cutaneous petechiae and purpura.**

(*Am J Dis Child* 134:354-355, 1980)

Although *Neisseria meningitidis* is a well-known pathogen of infancy and childhood, it is not usually considered as being among those organisms causing infectious disease during the neonatal period.[1,2] In this report, we describe a healthy infant with fulminant meningococcemia to emphasize that this organism must be considered in the differential diagnosis of sepsis in the neonate.

REPORT OF A CASE

This 25-day-old male infant was referred to the emergency ward having vomited the previous evening, become febrile (39.6 °C), and irritable. His mother was a healthy woman whose term pregnancy, labor, and delivery were uncomplicated. The child's early neonatal course was unremarkable except for nasal congestion that had developed ten days prior to admission.

On arrival in the emergency ward, the infant's vital signs included a temperature of 39.6 °C rectally, a pulse rate of 210 beats per minute, an arm cuff blood pressure of 74 mm Hg (palpation), and respirations of 24/min. The extremities were mottled and cool; he appeared pale, toxic, and irritable. Small, macular, purplish lesions (<1 × 1 cm) were scattered over the thighs, anterior thorax, right axilla, and left shoulder. Results of the neurological examination were normal except for irritability, increased tone, and hyperactive, symmetrical reflexes throughout.

Initial laboratory data showed a WBC count of 3,600/cu mm with 12 polymorphonuclear leukocytes, 11 band forms, 72 lymphocytes, one myelocyte, three metamyelocytes, and zero eosinophils. The platelet count was 286,000/cu mm, and a capillary blood sample (patient in room air) showed a Po_2 of 52 mm Hg, a Pco_2 of 34 mm Hg, and a pH of 7.28. Normal studies included a chest roentgenogram and determinations for hemoglobin, prothrombin time (PT), partial thromboplastin time (PTT), serum electrolytes, BUN, osmolality, and calcium levels, and urinalysis. The blood glucose level was 66 mg/dL. Gram's stain of the buffy coat and CSF showed no bacteria, whereas material from a purpuric lesion contained polymorphonuclear leukocytes without organisms. The CSF had four WBCs per cubic millimeter (all lymphocytes) and 35 RBCs per cubic millimeter, with a glucose level of 49 mg/dL and protein concentration of 30 mg/dL. An ESR was not determined.

The admitting diagnosis was septicemia; and oxacillin sodium (200 mg/kg/day), gentamicin sulfate (7.5 mg/kg/day), and 5% albumin (10 mL/kg) therapy was administered. Several hours after admission, larger purpuric lesions were apparent on the face, trunk, and extremities. Meningococcemia was strongly suspected at this time. Ampicillin sodium was added to the regimen for broader coverage pending culture results; hydrocortisone was given (150 mg/kg then 150 mg/kg/day in four doses); elective intubation was performed; central venous and arterial lines were placed; and volume expansion using packed RBCs and plasma was undertaken. Isoproterenol hydrochloride therapy was begun for hypotension; and sodium bicarbonate, in addition to other fluids, was required for persistent metabolic acidosis (pH was as low as 7.15). A potassium infusion was also begun for hypokalemia (serum potassium levels decreased from 4.7 to 2.9 mEq/L seven hours after admission).

The platelet count decreased to 17,000/cu mm, with a PT greater than 18 s and PTT greater than 100 s. Gross hematuria and oozing of blood from cutdown sites developed. Therefore, in addition to receiving fresh frozen plasma, the baby underwent a 1½-volume exchange transfusion with fresh heparinized blood. One unit of platelets was given before and after the exchange transfusion.

Dopamine hydrochloride therapy was begun because of declining urine output and persistent hypotension present during the first 24 hours of admission (systolic pressure ranged from 42 mm Hg to values between 70 to 80 mm Hg on days 2 and 3). Anuria and azotemia ensued, and peritoneal dialysis was initiated. This was continued for six days until renal function returned.

On the fifth day, a grade 3/6 systolic murmer was first noted. The pulses were bounding, the central venous pressure increased to 20 mm Hg, and the liver span increased by 4 cm. A chest roentgenogram was compatible with pulmonary edema, and the clinical diagnosis of patent ductus arteriosus was suggested. Neither myocarditis nor pericarditis was suspected by clinical or ECG findings. Therapy included isoproterenol, more vigorous volume removal by peritoneal dialysis, and respiratory support. As diuresis continued during the following 48 hours, his condition improved noticeably. Extubation was accomplished on the 13th day at which time the cardiac murmur had disappeared and the chest roentgenogram had returned to normal.

The PT and PTT were normal by 3½ days, and the platelet count had reached 114,000/cu mm by seven days. Heparin sodium was not used therapeutically at any time, except during the exchange transfusion. Hepatomegaly with cholestasis was a prominent feature. The total serum bilirubin level peaked at 12.0 mg/dL on the third day and declined steadily to 3.5 mg/dL on the ninth day and to 1.0 mg/dL on the 16th day; the SGOT and serum alkaline phosphatase levels remained normal.

Neurologically, his course was complicated by seizure activity on the sixth day characterized by eyelid and twitching in the right leg and by staring episodes. After resolution of his metabolic abnormalities, an EEG on day 15 displayed considerable rhythmic activity for age but was otherwise normal (an EEG on day 6 had been diffusely abnormal).

Neisseria meningitidis, group B, sensitive to sulfadiazine, was identified in both sets of blood cultures and in the CSF; cultures of bladder urine, throat, and stool were negative. He received penicillin G (400,000 units/kg/day) to complete a ten-day course from the time of initiation of oxacillin therapy. Cultures of blood and CSF taken on the tenth day were negative, and the CSF at that time had ten WBCs per cubic millimeter (one mononuclear and

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nine lymphocytes), zero RBCs, a protein level of 203 mg/dL, and a glucose level of 50 mg/dL.

Close contacts were identified and they along with the infant, the mother, and the father received rifampin prophylaxis; cultures were not taken of these individuals to determine their carriage status.

After his convalescence, the baby was discharged on a regimen of phenobarbital but was still hypotonic with poor visual pursuit. At 6 months of age, he was seen for repeated neurological evaluation. Two seizures had occurred since discharge, the last at age 3½ months. His developmental level was assessed as being 4 to 5 months of age. Moderate hypertonia of the upper extremities was noted, but vision seemed intact.

COMMENT

This infant experienced meningococcemia and meningitis with disseminated intravascular coagulation (DIC), leukopenia, probable acute tubular necrosis and renal failure, cardiac failure (probably secondary to a newly opened ductus arteriosus), and neurological dysfunction. That this constellation of initial problems gave him a grave prognosis was documented by Stiehm and Damrosch[3] in their retrospective study of 63 pediatric patients with meningococcemia. A very poor prognosis was associated with the presence of three or more of the five following features: the presence of petechiae for less than 12 hours prior to admission, the presence of shock (systolic blood pressure 70 mm Hg or less), a low or normal WBC count (< 10,000/cu mm), the absence of meningitis (WBCs < 20/cu mm in the CSF), and a low or normal sedimentation rate (< 10 mm/hr).

The early therapy provided for this infant was essentially that for Gram-negative sepsis with shock. Corticosteroids were used, but their use for the endotoxin shock associated with meningococcemia remains controversial.[4] He also received, in addition to other measures for DIC, an exchange transfusion and a therapeutic maneuver considered by some to be effective and safe for DIC in the neonate.[5]

Of interest was the hypokalemia. This has been observed in the first hours after admission in a group of 20 patients with meningococcemia, aged 9 months to 13 years, as a feature in those with hypotension (11 of 12 were hypokalemic, one not having had a potassium level measured). The remaining eight without hypotension did not have serial potassium measurements.[6]

To our knowledge, up to 1966, only 19 neonates with meningococcal disease had been described, and Stiehm and Damrosch[7] emphasized their comparatively benign course in their summary article. They discussed a 7-day-old infant that acquired group B meningococcal meningitis in the well-baby nursery, presumably from its mother's respiratory tract.[7]

To our knowledge, since 1966, only two other case reports of meningococcemia in the neonatal age group have appeared; both infants died. In the first case, a mother with meningococcal vaginitis may have transmitted the organism to her infant who died at 2 days of age with meningococcemia. Group C meningococci were recovered from the mother's lochia and pharynx and from the CSF and lung of the infant at postmortem examination.[8] Recently, a second case was reported in which fatal meningococcemia in a 15-day-old infant was associated with colonization of the maternal cervix.[9]

The incidence of disease has been shown to correlate with the absence of bactericidal antibodies to *N meningitidis*; more than 50% of the newborns have bactericidal titers of at least 1:4 against one or more test strains.[10] These antibodies would seem to be acquired transplacentally by those infants in whose mothers natural immunity had developed previously.[11] Placental transfer of antibodies to *N meningitidis* of groups A and C has recently been demonstrated, but antibody was not invariably found in infants of mothers who were immunized and seroconverted.[12]

The mode of acquisition of the organism in infected neonates is uncertain. Although two of the aforementioned cases suggest that intrapartum transmission via the maternal genitourinary tract might be important; genitourinary and anal carriage of *N meningitidis* in women is rare.[13,14]

It is clear from this case and the others cited that meningococcal disease does occur in neonates. Physicians caring for infants in this age group should consider this diagnostic possibility whenever cutaneous petechial or purpuric lesions are observed in a neonate.

Manginello et al[15] have very recently described a 2-week-old infant with meningococcemia and meningococcal meningitis who was successfully treated. They state that all close contacts should continue to be screened for respiratory and genitourinary colonization; but we should like to emphasize that close contacts be treated with an appropriate agent.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S, Polycillin-N, Principen/N.*
Dopamine hydrochloride—*Intropin.*
Gentamicin sulfate—*Garamycin.*
Rifampin—*Rifadin, Rimactane.*

References

1. Klein JO, Marcy SM: Bacterial infections, in Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant.* Philadelphia, WB Saunders Co, 1976, p 747.
2. Groover RV, Sutherland JM, Landing BH: Purulent meningitis of newborn infants: Eleven-year experience in the antibiotic era. *N Engl J Med* 264:1115-1121, 1961.
3. Stiehm ER, Damrosch DS: Factors in the prognosis of meningococcal infection: Review of 63 cases with emphasis on recognition and management of the severely ill patient. *J Pediatr* 68:457-467, 1966.
4. Hodes HL: Endotoxin shock, in Smith CA (ed): *The Critically Ill Child,* ed 2. Philadelphia, WB Saunders Co, 1977, pp 25-45.
5. Gross S, Melhorn DK: Exchange transfusion with citrated whole blood for disseminated intravascular coagulation. *J Pediatr* 78:415-419, 1971.
6. Mauger DC: Hypokalemia as a consistent feature of fulminant meningococcal septicaemia. *Aust Paediatr J* 7:84-86, 1971.
7. Stiehm ER, Damrosch DS: Neonatal meningococcal meningitis: Report of a case acquired in the nursery. *J Pediatr* 68:654-656, 1966.
8. Sunderland WA, Harris HH, Spence DA, et al: Meningococcemia in a newborn infant whose mother had meningococcal vaginitis. *J Pediatr* 81:856, 1972.
9. Jones RN, Slepack J, Eades A: Fatal neonatal meningococcal meningitis: Association with maternal cervical-vaginal colonization. *JAMA* 236:2652-2653, 1976.
10. Goldschneider I, Gotschlich EC, Artenstein MS: Human immunity to the meningococcus: I. The role of humoral antibodies. *J Exp Med* 129:1307-1326, 1969.
11. Goldschneider I, Gotschlich EC, Artenstein MS: Human immunity to the meningococcus: II. Development of natural immunity. *J Exp Med* 129:1327-1348, 1969.
12. Carvalho AD, Giampaglia CM, Kimura H, et al: Maternal and infant antibody response to meningococcal vaccination in pregnancy. *Lancet* 2:809-811, 1977.
13. Faur YC, Weisburd MH, Wilson MD: Isolation of *Neisseria meningitidis* from the genitourinary tract and anal canal. *J Clin Microbiol* 2:178-182, 1975.
14. Judson FN, Ehret JM, Eickhoff TC: Anogenital infection with *Neisseria meningitidis* in homosexual men. *J Infect Dis* 137:458-463, 1978.
15. Manginello FP, Pascale JA, Wolfsdorf J: Neonatal meningococcemia. *AJDC* 133:651-652, 1979.

Metastatic Complications of *Fusobacterium necrophorum* Sepsis

Two Cases of Lemierre's Postanginal Septicemia

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• **We have recently encountered two instances of septicemia due to *Fusobacterium necrophorum* in adolescents. The presence of severe exudative pharyngitis in both patients pointed to the upper respiratory tract as the probable portal of entry. In one case, metastatic infection was manifested by multiple septic pulmonary emboli with associated pleural effusions. In the other case, diffuse encephalopathy and septic arthritis of the left shoulder and hip occurred. Unilateral neck pain, persistent bacteremia, and prolonged fever despite appropriate antibiotics were consistent with the presence of septic jugular thrombophlebitis in both patients. "Postanginal septicemia" caused by *F necrophorum*, described by Lemierre in the preantibiotic era, was undoubtedly the syndrome manifested by these patients. This condition, formerly uniformly fatal, can readily be diagnosed when anaerobic techniques are used for blood culture, but requires prolonged antibiotic therapy for cure.**

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Although anaerobic Gram-negative bacilli of the family Bacteroidaceae are increasingly being recognized in septicemic illnesses,[1-4] the pathogenic potential of these organisms was well known in the preantibiotic era. A clinical entity known as "postanginal septicemia" in which oropharyngeal infection is complicated by local septic thrombophlebitis, continuous anaerobic bacteremia, and multiple sites of metastatic infection was summarized in 1936 by Lemierre,[5] "The appearance and repetition several days after the onset of a sore throat... of severe pyrexial attacks with an initial rigor, or still more certainly the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible."

The most frequent causal agent in this syndrome, known to Lemierre[5] as *Bacillus funduliformis*, is now classified as *Fusobacterium necrophorum*. We have recently cared for two adolescent patients with anaerobic sepsis due to this organism. Their clinical features were remarkably similar to Lemierre's early description of postanginal sepsis. Despite appropriate antibiotic therapy, both patients had dramatic and prolonged febrile illnesses associated with persistent bacteremia and metastatic spread of infection.

REPORT OF CASES

CASE 1.—A 16-year-old girl was hospitalized with a three-day history of sore throat, unilateral neck pain, and dysphagia, and two days of fever and vomiting. On admission, she was lethargic and appeared acutely ill. Her temperature was 38.6 °C. Her left tonsil was enlarged and covered by gray exudate. The left side of her neck, along the anterior border of the sternocleidomastoid muscle, was tender and swollen.

Laboratory values were as follows: hemoglobin, 12.5 g/dL; hematocrit, 38.2%; and peripheral WBCs, 11,100/cu mm, with 65% polymorphonuclear leukocytes, 25% band forms, 4% lymphocytes, 5% monocytes, and 1% eosinophils. Urinalysis showed moderate proteinuria. The urinary sediment contained 60 to 70 WBCs per high-power field (HPF). Chest and lateral neck roentgenograms were normal.

After admission, she continued to have sore throat, high temperatures up to 40 °C, and intermittent shaking chills. Throat cultures were negative for group A β-hemolytic streptococci. Urine cultures were sterile. No serum heterophile antibody was detectable. On the third hospital day, Gram-negative bacilli were observed in the thioglycollate broth of the admission blood culture. Therapy with intravenous cephalothin sodium succinate (170 mg/kg/day), gentamicin sulfate (5 mg/kg/day), and chloramphenicol (85 mg/kg/day) was begun. On the fifth hospital day, the bacilli were identified as obligate anaerobes, and therapy was changed to intravenous penicillin G potassium (250,000 units/kg/day). A chest roentgenogram on the fifth hospital day showed bibasilar infiltrates and pleural effusions. A right thoracentesis yielded serous fluid that was negative by Gram's stain and sterile on aerobic and anaerobic culture. The fluid contained 3,300 WBCs per cubic millimeter (all polymorphonuclear leukocytes) and had a specific gravity of 1.026 and total protein content of 4.1 g/dL. Spiking fever persisted for the first ten hospital days and then gradually defervesced during the next eight days. Serial chest roentgenograms demonstrated resolution of the pleural effusions and development of multiple pneumatoceles (Fig 1). She received a total of 25 days of therapy with intravenous penicillin G, followed by an additional three months of therapy with oral penicillin V. During this time, the pneumatoceles completely resolved.

The anaerobic organism present in each of the five blood cultures obtained during her first four days of hospitalization was identified as *F necrophorum*.[6] Anaerobic broth dilution susceptibility testing of the isolate to penicillin G, using thioglycollate broth supplemented with 10% horse serum, demonstrated minimal inhibitory and bactericidal concentrations of 0.04 μg/mL.[7]

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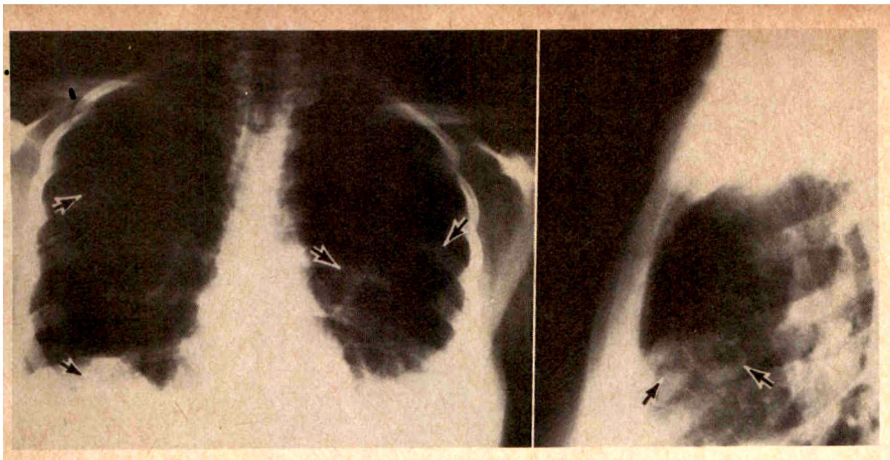

Fig 1.—Chest roentgenogram of case 1 obtained on 13th day of illness. Pneumatoceles are present in both lung fields.

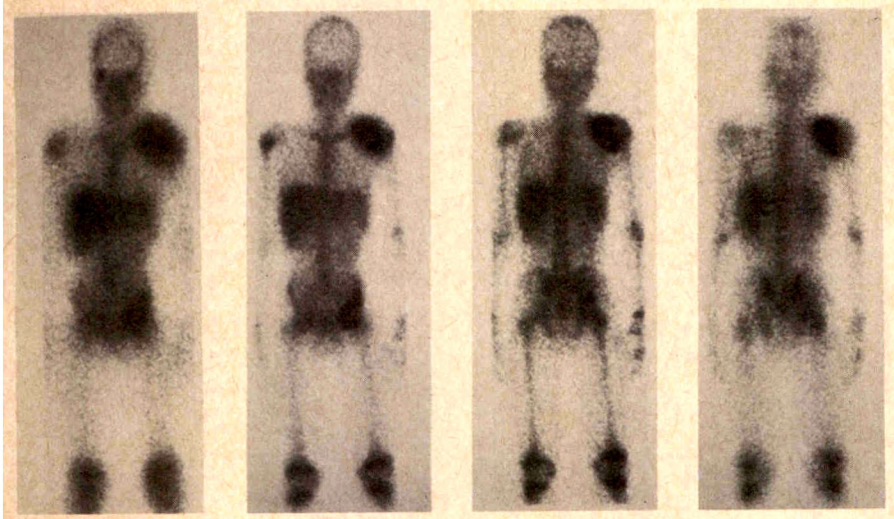

Fig 2.—Tomographic gallium 67 scans of case 2 obtained on tenth day of illness. Increased radionuclide uptake is evident in left shoulder and hip joints.

CASE 2.—A 12-year-old boy was hospitalized with a five-day history of sore throat, three days of fever and lethargy, and one day of diplopia and pain in the left knee, shoulder, and neck. On admission, he was lethargic and disoriented. His temperature was 39.5 °C. Both tonsils were erythematous with gray membranes, and the left side of his neck was tender. The liver was enlarged to 5 cm below the right costal margin. The left knee, hip, and shoulder were tender, with limitation of motion but without palpable joint effusions. Neurologic examination disclosed an attentional defect, hallucinations, and dysconjugate gaze consistent with a diffuse encephalopathy.

Laboratory findings were as follows: hemoglobin, 12.4 g/dL; hematocrit, 38%; and WBCs, 9,200/cu mm, with 45% polymorphonuclear leukocytes, 32% band forms, 5% metamyelocytes, 14% lymphocytes, and 4% monocytes. The urinary sediment contained 20 to 30 RBCs and four to six WBCs per HPF. Cerebrospinal fluid was clear and colorless with no cells, glucose level was 92 mg/dL, and protein concentration was 15 mg/dL. The Westergren ESR was 125 mm/hr. Throat cultures were negative for group A β-hemolytic streptococci, although serum antistreptolysin O and antihyaluronidase titers were 1:640 and 1:512, respectively. Serum heterophile antibody titers were negative. A brain scan and roentgenograms of the chest, skull, neck, left leg, and left shoulder were normal. An EEG demonstrated diffuse slowing.

Intravenous penicillin G potassium therapy (100,000 units/kg/day) was started on admission. Lethargy and high temperatures to 41 °C persisted. On the third hospital day, Gram-negative filamentous bacilli were isolated from the thioglycollate broth of the admission blood culture. Intravenous therapy with ampicillin sodium (300 mg/kg/day), gentamicin sulfate (5 mg/kg/day), and chloramphenicol sodium succinate (60 mg/kg/day) was begun. When the blood culture isolate proved to be an obligate anaerobe, therapy was changed to penicillin G potassium (300,000 units/kg/day) and chloramphenicol sodium succinate (100 mg/kg/day). High fever persisted for the first ten hospital days, but steady improvement in sensorium and neurologic findings occurred. Radionuclide scans with gallium 67 showed increased uptake in the left shoulder and iliac bone (Fig 2); technetium 99 pyrophosphate scans confirmed the presence of inflammatory lesions of the left shoulder, hip, and knee. With clinical improvement and in the absence of effusions of the involved joints, arthrocentesis was deferred. A total of three weeks of intravenous penicillin G and chloramphenicol therapy was given, followed by an additional two months of oral penicillin V therapy. All symptoms resolved completely.

The anaerobic isolates from blood cultures obtained on the first, third, and fourth hospital days were identified as *F necrophorum*. By anaerobic disk techniques, the organism proved to be sensitive to both penicillin and chloramphenicol.[7] Anaerobic broth dilution susceptibility testing to penicillin G showed a minimal inhibitory concentration of 0.08 μg/mL and minimal bactericidal concentration of 0.15 μg/mL.

COMMENT

Fusobacteria are obligately anaerobic, nonsporulating, Gram-negative bacilli of the family Bacteroidaceae. Their characteristic fusiform morphology is distinctive, but modern techniques of speciation are based on identification of specific volatile fatty acid metabolic by-products by gas-liquid chromatography.[6] Fusobacteria are major contributors to the normal flora of the oral cavity, the female genital tract, and, to a lesser extent, the gastrointestinal tract. With *Treponema vincentii*, they were classically described in localized "fusospirochetal" infections of the oral cavity, such as Vincent's angina ("false diphtheria") and Vincent's stomatitis ("trench mouth"). When modern anaerobic techniques have been used for diagnosis, they have been frequently isolated from dental abscesses, peritonsillar abscesses, aspiration pneumonias, and lung abscesses, and, less commonly, from appendiceal abscesses, liver abscesses, and tuboovarian abscesses.[8]

Of the 17 known species of *Fusobacterium*, *F necrophorum* and *F nucleatum* have been most frequently recovered in anaerobic sepsis. Although numerous descriptions of serious infections caused by *F necrophorum* appear in the literature of the preantibiotic era, bacteriologic uncertainty exists regarding many of these cases

because of varying criteria for speciation of isolates. Some 52 synonyms and probable synonyms for this species, of which *Sphaerophorus necrophorus*, *B funduliformis*, and *Fusiformis necrophorus* are encountered frequently, add to the difficulty of interpreting this early work.[8]

In a recent prospective survey of anaerobic infections in pediatric patients, Dunkle et al[9] encountered 41 instances of anaerobic bacteremia, of which three were due to fusobacteria (all *F nucleatum*). In a similar study, Thirumoorthi et al[10] found 34 instances of anaerobic bacteremia, of which two were due to fusobacteria (one *F glutinosum*, one not speciated). The nature of these fusobacterial septicemias was not further specified. Several case reports of septic illness from which fusobacteria were recovered have also appeared in the pediatric literature in recent years. Oleske et al[11] described a 14-year-old boy with pharyngitis, peritonsillar abscess formation, and multiple lung abscesses. *Fusobacterium necrophorum* was isolated from the neck mass in pure culture, although multiple blood cultures were negative.

Rubenstein et al[12] described a 7-year-old boy in whom unilateral cervical mass, pericarditis, and *F gonidiaformans* bacteremia developed after tonsillectomy and adenoidectomy. Two patients with anaerobic meningitis and bacteremia caused by fusobacteria (one *F gonidiaformans* and one not speciated) were described by O'Grady and Ralph.[13] In one of their cases, otitis media and acute mastoiditis were the probable source of bacteremia. In the other, exudative pharyngitis was a prominent associated finding. All four of these patients had prompt therapeutic responses to appropriate antibiotics. However, in three instances relapses occurred after short initial courses of therapy.

Our case 1 had febrile illness characterized by exudative tonsillitis, unilateral neck pain, vomiting, and sterile pyuria. Multiple septic pulmonary emboli developed during hospitalization. *Fusobacterium necrophorum* bacteremia persisted for four days, despite the initiation of appropriate antibiotic therapy. Although the infecting organism was shown to be quite sensitive to penicillin G, the patient's hospital course was prolonged, and recovery was gradual.

Case 2 also had multisystem involvement when first seen, with conspicuous CNS and skeletal system involvement tending to overshadow the presence of exudative pharyngitis. *Fusobacterium necrophorum* bacteremia also persisted for four days, despite therapy with intravenous penicillin G and chloramphenicol, to which the isolate was subsequently proved to be sensitive. Chloramphenicol was used in the regimen based on the patient's neurologic involvement and pending the results of definitive antibiotic susceptibility testing. The patient's encephalopathy cleared during the first week after initiation of therapy, but joint symptoms continued until shortly before discharge in the fifth week of illness.

In both cases, the findings of exudative pharyngotonsillitis, unilateral neck pain and swelling, persistent bacteremia, and embolic phenomena were consistent with the presence of septic thrombophlebitis of the tonsillar and internal jugular veins. In the cases reported by Lemierre,[5] this finding was uniformly present at autopsy and was considered by him to be central in the pathogenesis of the condition.

The slow therapeutic response to appropriate antibiotics in our two patients was particularly worrisome. Fusobacteria, as a rule, are quite sensitive to penicillins, chloramphenicol, clindamycin, and metronidazole.[14] Our cases were not exceptional. In fact, during treatment of case 2, peak serum bacteristatic activity was present in a dilution of 1:1,024. It is probable that the prolonged febrile courses we observed were related to the presence of metastatic suppurative foci secondary to septic thrombophlebitis. These foci were not readily amenable to surgical drainage. In a similar situation, Josey and Staggers[15] observed rapid clinical improvement in 42 of 46 cases of septic pelvic thrombophlebitis, 15 of which had concomitant metastatic pulmonary infection, when heparin sodium was added to appropriate antibiotic regimens. No controlled trials are available, however, that establish the value of this adjunctive therapy. In retrospect, the use of heparin would probably have been appropriate in our case 1; in case 2, the predominant neurologic involvement made us hesitate to use anticoagulant drugs.

The distinctive syndrome of "postanginal sepsis" due to *F necrophorum* should be borne in mind by the clinician faced with septic illness complicating oropharyngeal infection. Prolonged antibiotic therapy seems to be necessary for eradication of these serious anaerobic infections.

William L. Schey, MD, and V. Yun Ryo, MD, gave permission to reproduce the roentgenograms. Earnestine Cloyd, MS, performed the anaerobic susceptibility testing. Madeline Murphy provided secretarial assistance.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S, Polycillin-N, Principen/N.*
Cephalothin sodium—*Keflin.*
Gentamicin sulfate—*Garamycin.*
Metronidazole—*Flagyl.*

References

1. McVay LV, Sprunt DH: Bacteroides infections. *Ann Intern Med* 36:56-76, 1952.
2. Tynes BS, Frommeyer WB: Bacteroides septicemia: Cultural, clinical, and therapeutic features in a series of 25 patients. *Ann Intern Med* 56:12-26, 1962.
3. Felner JM, Dowell VR: "Bacteroides" bacteremia. *Am J Med* 50:787-796, 1971.
4. Chow AW, Guze LB: *Bacteroidaceae* bacteremia: Clinical experience with 112 patients. *Medicine* 53:93-126, 1974.
5. Lemierre A: On certain septicemias due to anaerobic organisms. *Lancet* 1:701-703, 1936.
6. Holdeman LV, Moore WEC: *Anaerobe Laboratory Manual*, ed 3. Blacksburg, Va, VPI Anaerobe Laboratory, Virginia Polytechnic Institute and State University, 1975.
7. Sutter VL, Vargo VL, Finegold SM: *Wadsworth Anaerobic Bacteriology Manual*, ed 2. Los Angeles, University of California Press, 1975.
8. Finegold SM: *Anaerobic Infections in Human Disease*. New York, Academic Press Inc, 1977.
9. Dunkle LM, Brotherton TJ, Feigin RD: Anaerobic infections in children: A prospective survey. *Pediatrics* 57:311-320, 1976.
10. Thirumoorthi MD, Keen BM, Dajani AS: Anaerobic infections in children: A prospective study. *J Clin Microbiol* 3:318-323, 1976.
11. Oleske JM, Starr SE, Nahmias AJ: Complications of peritonsillar abscess due to *Fusobacterium necrophorum*. *Pediatrics* 57:570-572, 1976.
12. Rubenstein E, Onderdonk AB, Rahal JJ: Peritonsillar infection and bacteremia caused by *Fusobacterium gonidiaformans*. *J Pediatr* 85:673-675, 1974.
13. O'Grady LR, Ralph ED: Anaerobic meningitis and bacteremia caused by *Fusobacterium* species. *Am J Dis Child* 130:871-873, 1976.
14. Finegold SM, Bartlett JG, Chow AW, et al: Management of anaerobic infections. *Ann Intern Med* 83:375-389, 1975.
15. Josey WE, Staggers SR: Heparin therapy in septic pelvic thrombophlebitis: A study of 46 cases. *Am J Obstet Gynecol* 120:228-233, 1974.

Spectinomycin Therapy for Gonorrhea in Prepubertal Children

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• **Twenty-six episodes of gonococcal urethritis or vulvovaginitis in 24 prepubertal patients were each treated with a single intramuscular (IM) dose of spectinomycin hydrochloride. Twenty-five episodes were treated successfully, and there were no side effects from this therapy. All tested isolates of *Neisseria gonorrhoeae* were susceptible in vitro to spectinomycin, and all serum levels one hour after therapy were in at least two-fold excess of the observed minimum inhibitory concentrations. Two patients had symptomatic and two had asymptomatic postgonococcal anogenital infections with *Chlamydia trachomatis*. A single dose of IM spectinomycin is a safe and efficacious regimen for uncomplicated gonococcal infection in prepubertal children who are penicillin-allergic or who have infections unresponsive or resistant to other antimicrobials, but it is not effective against incubating syphilis or chlamydial infection.**

(*Am J Dis Child* 134:359-363, 1980)

The recognition of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) in 1976[1] and subsequent worldwide dissemination of these strains[2] have added urgency to the search for safe and effective alternatives to penicillin G and other β-lactamase-susceptible antibiotics for the therapy of gonococcal infections. As of March 1979, PPNG strains had been reported in 27 countries and in 31 states.[2] They have been associated with a wide spectrum of clinical manifestations, including one case report of vulvovaginitis in a prepubertal girl.[3]

The most recent Public Health Service recommendations for treatment of uncomplicated gonorrhea in adults suggest the use of spectinomycin hydrochloride for penicillin-allergic patients who are also intolerant of tetracycline hydrochloride, for all patients who fail to respond to initial therapy with a penicillin or tetracycline, and for all PPNG-infected patients and their sexual contacts.[4] Spectinomycin has been extensively studied in adults during the past 17 years, initially as the sulfate salt (actinospectocin) and subsequently as the currently available dihydrochloride pentahydrate salt. It has been a well-tolerated and effective drug for uncomplicated anogenital gonorrhea.[5-13] To our knowledge, there is no information on the use of spectinomycin in pediatric patients with gonococcal infections except for the one case previously mentioned.[3] The purpose of this study was to evaluate the efficacy of spectinomycin hydrochloride in uncomplicated gonorrhea in children.

SUBJECTS AND METHODS

Patient Selection

Eligible patients were those between 1 and 15 years of age who were initially evaluated for urethritis or vulvovaginitis, thought to be gonococcal on clinical and bacteriologic grounds. Patients were initially seen in the ambulatory care clinic at the Children's Medical Center or in the pediatric emergency room at Parkland Memorial Hospital in Dallas. Entry into the study was based on demonstration of abundant, Gram-negative, intracellular diplococci in genital secretions or cultural confirmation of *N gonorrhoeae* if Gram-stained specimens were not diagnostic. Children were scheduled for two follow-up visits at four to six days and ten to fourteen days for repeated physical examinations and test-of-cure cultures. Written informed consent for entry into the study and for spectinomycin treatment was obtained from the parents. The patients and attending parents were interviewed by a pediatric social worker and were reported to the Dallas City Health Department venereal disease control clinic.

Laboratory Procedures

Anal, pharyngeal, and genital swabs were collected at each visit and inoculated onto blood agar, chocolate agar, and modified Thayer-Martin agar containing vanco-

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Reprints not available.

mycin, colistin, and nystatin. Vaginal and anal cultures were also inoculated onto eosin-methylene blue agar. Thayer-Martin and chocolate agar plates were incubated in candle extinction jars. Isolation of *N gonorrhoeae* was confirmed by growth of Gram-negative diplococci that fermented dextrose and failed to ferment sucrose or maltose in cystine trypticase agar. Genital, anal, and pharyngeal swabs were also placed in sucrose-phosphate buffer containing gentamicin and amphotericin B and frozen at −70 °C for chlamydial cultures. *Chlamydia trachomatis* isolation was made in 5-iodo-2-deoxyuridine-treated McCoy cells by the method of Wentworth and Alexander.[14]

Serologic tests for syphilis (VDRL) were obtained at the initial treatment visit and were repeated between two and three months after therapy.

Susceptibility testing was done by agar dilution using penicillin G and spectinomycin laboratory standards. Loopfuls of an overnight growth on chocolate agar were suspended in 1.0 mL of Mueller-Hinton broth with 1% of a broth supplement (IsoVitaleX) to a turbidity approximating 10^9 organisms per milliliter. A final dilution of 10^4 to 10^5 colony-forming units per milliliter was plated on chocolate agar (GC agar base with 2% hemoglobin and 1% IsoVitaleX) containing two-fold dilutions of the antibiotics tested. Inhibitory end points were read after 24 hours' incubation at 36 °C in candle extinction jars. In addition, disk diffusion sensitivities using 100-μg spectinomycin disks were performed using a modified Kirby-Bauer method, with the previously mentioned inoculum and medium. Isolates from treatment failures and those showing decreased penicillin sensitivity (minimal inhibitory concentration [MIC] ≥ 1.25 μg/mL) were tested for β-lactamase activity using a rapid iodometric paper strip test.[15]

Serum specimens were obtained from patients one hour after injection of spectinomycin. Antibiotic levels were determined by a standardized plate microbioassay using *Escherichia coli*.

Treatment

Patients received a single dose of 40 mg/kg of spectinomycin hydrochloride injected intramuscularly into the buttock or anterolateral thigh. Volumes greater than 3.0 mL were divided and administered in two injection sites.

RESULTS

Between February 1978 and November 1978, 26 episodes of gonococcal urethritis or vulvovaginitis in 24 patients were treated. All patients were prepubertal (defined as absence of breast development in girls and testicular length <4 cm in boys). One 7-year-old boy had three episodes of gonococcal urethritis during a 4½ month period. Ages ranged from 2 years, 4 months to 12 years, 11 months, with an average of 7 years. The mean age of female patients (67 months) was significantly less than that of male patients (102 months) ($P < .01$; Student's t test, $t = 2.61$; $df = 24$).

All patients were symptomatic, with the most common symptom being a genital discharge (present in all 26 episodes). In the boys, 11 of 13 episodes were accompanied by dysuria. One boy had balanitis and four had erythema and edema of the urethral meatus. Six female patients had complaints of dysuria, and three others had urgency or increased frequency of urination. Two had lower abdominal pain by history, but neither had adnexal tenderness or masses. Abnormal physical findings in girls were limited to vaginal discharges (13 of 13 patients), which ranged from white and mucousy to thick, green, and malodorous, and to vulvar and introital erythemas (nine of 13). In eight episodes, patients had been symptomatic for only one day; and in 19 (73%), symptoms had been present for one week or less. Two female patients had discharges for three and for four weeks before treatment.

Smears of genital discharges were initially positive in all 26 episodes. Genital cultures confirmed *N gonorrhoeae* infection in 23 instances. In three cases, Gram-negative diplococci were isolated in pure growth on Thayer-Martin media, but they could not be confirmed as *N gonorrhoeae* by carbohydrate fermentations because of technical problems. Two of these patients were siblings of a third child (not in this study) who had had confirmed gonococcal urethritis one week earlier. All three were believed to have gonococcal infection on the basis of clinical characteristics, Gram's-stain findings, epidemiologic features, and clinical responses. None of 22 pretreatment rectal cultures were positive for the gonococcus. *Neisseria gonorrhoeae* was isolated from the pharyngeal culture of a 6-year, 11-month-old girl, but the remaining 21 throat cultures were negative. No patient initially had a reactive VDRL test, and follow-up serologic tests obtained from 14 patients remained nonreactive.

At least one follow-up evaluation was made in each patient. A total of 24 patients had cessation of symptoms within 96 hours of therapy, including 20 who were symptom-free within 48 hours. Two patients, one boy and one girl, had continued purulent genital discharge when seen at follow-up six and four days, respectively, after therapy. The 7-year-old boy had repeated urethral smear and culture positive for *N gonorrhoeae*. His organism had an MIC to spectinomycin of 20 μg/mL both before and after treatment and was β-lactamase-negative. The serum level of spectinomycin one hour after injection was assayed as 62 μg/mL. He responded clinically and bacteriologically to oral tetracycline hydrochloride, 40 mg/kg/day for four days. He denied reexposure and was considered the only treatment failure. However, he subsequently had two more episodes of gonococcal urethritis successfully treated with spectinomycin, and it is possible that his earlier "failure" was actually due to reinfection. All remaining patients were bacteriologically negative at the first (25/25) and second (23/23) follow-up examinations.

The 7-year-old girl with persistent nongonococcal vaginal discharge had positive rectal and vaginal cultures for *C trachomatis*. Her symptoms and positive chlamydial cultures continued for two weeks until her condition was treated with oral trisulfapyrimidines (120 mg/kg/day for ten days). An additional case of symptomatic postgonococcal genital infection owing to *C trachomatis* occurred in a 7-year-old boy who had recurrence of a thin, watery, urethral discharge 12 days after spectinomycin therapy. Two additional patients had asymptomatic postgonococcal chlamydial infection of the rectum and of the rectum and vagina.[16]

Minimal inhibitory concentrations of penicillin G and spectinomycin in 24

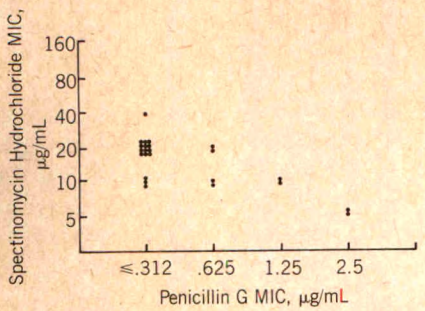

Fig 1.—Minimal inhibitory concentrations (MICs) of spectinomycin hydrochloride and penicillin G against *Neisseria gonorrhoeae* by agar dilution.

gonococcal isolates are shown in Fig 1. No isolates were β-lactamase-positive. Of the isolates, 87% had spectinomycin MICs of 10 or 20 µg/mL, with the median MIC being 20 µg/mL. There was no apparent direct or inverse correlation between penicillin and spectinomycin sensitivities.

The correlation between the disk zone of inhibition and the MIC for spectinomycin is shown in Fig 2. The line of regression was calculated by the method of least squares, expressing the MICs as relative values on the Y-axis (correlation coefficient was $-.458$, $.01 < P < .05$).

Serum levels of spectinomycin hydrochloride one hour after intramuscular (IM) injection of 40 mg/kg ranged from 22 µg/mL to 87.5 µg/mL. The arithmetic mean level was 64.3 ± 3.8 µg/mL (arithmetic mean ± SEM) and the median value was 72 µg/mL. Serial blood samples were available from three patients, and the results are shown in Fig 3. The drug was well tolerated in all patients, and no local or systemic side effects were reported.

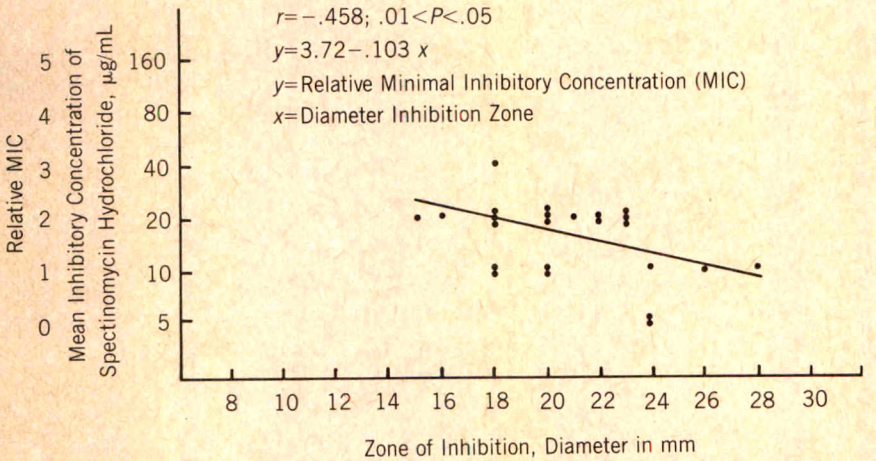

Fig 2.—Correlation of spectinomycin hydrochloride susceptibilities of *Neisseria gonorrhoeae* as determined by agar dilution and disk diffusion.

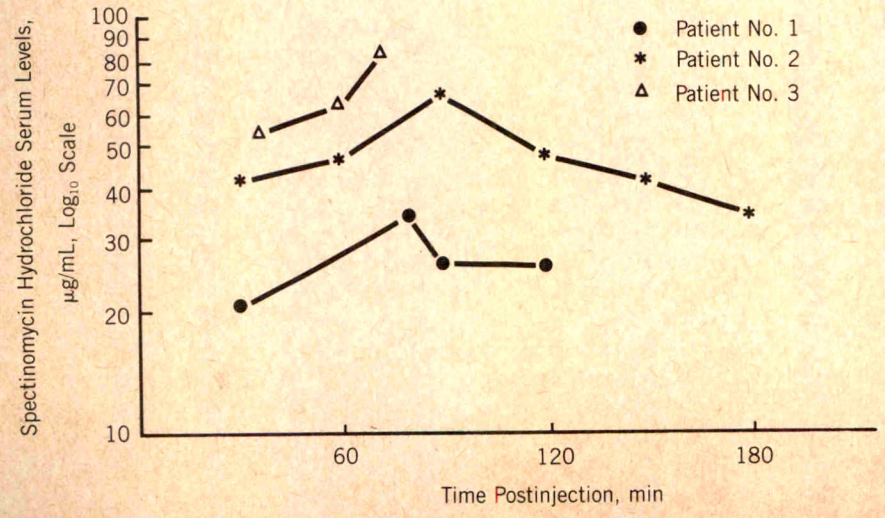

Fig 3.—Serial spectinomycin hydrochloride serum levels after 40 mg/kg intramuscular injection.

COMMENT

The cure rate (96.1%) in this series of pediatric patients is comparable with those previously reported in adults with anogenital infection.[5-13] The drug has had minimal toxic effects in adults and was uniformly well tolerated by subjects in this study. Although there were no PPNG isolates from patients in this study, several recent reports have shown spectinomycin to be curative against such strains,with success rates comparable with those seen with β-lactamase-negative isolates.[3,17,18]

The epidemiologic and clinical characteristics of this group of patients were similar to those previously reported from our hospitals.[19] The significantly different ($P < .01$) average ages between male and female patients were observed in the earlier study, and they may in part be due to the observation by Branch and Paxton[20] that children aged 2 to 9 years were most often exposed to infection by molestation within the family while children 10 years or older were most often infected by voluntary heterosexual activity. However, definite information concerning the source of infection was lacking in the majority of our patients, and this hypothesis cannot be confirmed. The previous treatment study showed high rates of anal (40%) and pharyngeal (17%) coinfection in pretreatment cultures. Only one patient in this series had pharyngeal gonococcal infection, and all anal cultures were negative for *N gonorrhoeae*. After the conclusion of this study, it was realized that the anal cultures were in fact rectal

cultures, owing to deeper insertion of cotton swabs, ie, beyond the anal crypts. This may explain the negative yield from this site because in all other respects, the patient populations were similar and the microbiologic methods identical in the two studies.

The range of in vitro susceptibilities of gonococci to spectinomycin in this study is somewhat higher than that noted by some previous investigators[6-8,10,12,21,22]; but it is similar to that in other studies,[9,13] in our previous study,[19] and in the Center for Disease Control National Gonorrhea Therapy Monitoring Study.[22] These discrepancies between studies may be due to the use of different antibiotic dilutions and to difficulties in standardizing inocula rather than to any true geographic or temporal susceptibility differences. Although some investigators have found a weakly positive correlation between penicillin and spectinomycin susceptibilities,[7,9,11,12] not all studies have shown such an association,[8] and none was evident in this study. Although PPNG isolates from the United States were relatively less susceptible to spectinomycin than non-PPNG strains, all had spectinomycin sensitivities ≤ 16 μg/mL.[18] No decreased spectinomycin susceptibility in PPNG isolates from the Far East compared with β-lactamase-negative Asian isolates was noted by Thornsberry et al.[23] Most importantly, there has been no association between increased treatment failure rates with spectinomycin and decreased penicillin sensitivity.[22]

Spectinomycin treatment failures have not been correlated with increasing in vitro resistance to the drug. Our one treatment failure had adequate serum levels of the antibiotic and was infected with an organism demonstrating in vitro sensitivities before and after therapy (MIC, 20 μg/mL). Although there have been three reported spectinomycin-resistant *N gonorrhoeae* isolates from clinical specimens[24,25] and high-level resistance is readily inducible in vitro, most treatment failures with this drug are due to an unknown mechanism and not to demonstrable intrinsic resistance.[12,22]

The occurrence of postgonococcal infections with *C trachomatis* has been noted in spectinomycin treatment studies in adults, with incidence rates from 7% to 27%.[5,22,26,27] Spectinomycin has no in vitro activity against *C trachomatis* at usually attainable serum concentrations. This fact, along with the drug's lack of efficacy against incubating syphilis, is one of its main disadvantages as a first-line drug for all uncomplicated gonococcal infections.

Disk agar-diffusion sensitivities of *N gonorrhoeae* have been performed infrequently because of the organism's slow, somewhat fastidious growth and because of the difficulty in standardizing inoculum size. The results obtained in this study are consistent with those obtained by Washington and Yu[28] when they examined disk sensitivities of coliform bacteria to spectinomycin. All isolates in our study had zone diameters greater than 14 mm, which concurs with the suggestion by Washington and Yu that zone diameters of less than 14 mm with a 100-μg spectinomycin disk be interpreted as showing resistance. The rather low correlation coefficient (−.458) may be due to the narrow range of spectinomycin susceptibilities and the small number of strains tested. Although Washington and co-worker's suggested interpretive zone diameters may be applicable to gonococcal sensitivities, it would be advisable to test for gonococcal spectinomycin susceptibility by more established agar dilution methods until larger numbers of isolates are examined in a well-standardized and highly reproducible fashion.

The serum spectinomycin levels in our patients were lower than those reported in adults after a single IM injection of 2.0 g.[26,29] (The 40 mg/kg dose used in our study would give a larger dose, on a weight basis, to a 70-kg adult than the commonly used 2.0-g dose). Brownlow et al[26] found an average serum concentration of 88.6 ± 33.9 μg/mL (mean ± SD) two hours after a single 2.0-g IM injection of the hydrochloride salt. An average level of 109.2 μg/mL was obtained in 12 adult volunteers one hour after injection (The Upjohn Company, unpublished data). In pediatric patients, Barry and Koch[30] reported one-hour serum levels of 60 and 80 μg/mL in two patients given 25 mg/kg of the sulfate salt intramuscularly, and an average of 30 mg/kg in five patients given 12.5 mg/kg. The serial serum levels from three of our patients (Fig 3) suggest that peak serum concentrations may have occurred later than one hour after injection. Despite the somewhat lower-than-expected levels observed in this study, the mean level at one hour was fourfold greater than the average MIC.

Spectinomycin has not been evaluated in extragenital or disseminated gonococcal infection in children. It has not been effective in oropharyngeal gonorrhea in adults.[13] There are no data on this drug's pharmacokinetics or toxicity in neonates, and its use in newborns cannot be recommended. Clinicians treating pediatric gonorrhea should restrict the use of spectinomycin to those clinical situations outlined in the published guidelines, and they should be aware that spectinomycin does not eradicate incubating syphilis and is not effective against concurrent infections with *C trachomatis*. Our study does support the recent PHS-recommended dose of 40 mg/kg for uncomplicated pediatric anogenital gonococcal infection. The therapeutic efficacy, safety, and in vitro gonococcal susceptibility patterns of spectinomycin in this series of pediatric patients are similar to results obtained previously in adults.[31]

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Edythe Woodman performed the antimicrobial susceptibility testing, Sharon Shelton performed the antibiotic assays, and Kathy Faust performed the cultures for *Chlamydia*.

Nonproprietary Name and Trademark of Drug

Spectinomycin hydrochloride—*Trobicin*.

References

1. Phillips I: β-Lactamase-producing, penicillin-resistant gonococcus. *Lancet* 2:656-657, 1976.

2. Center for Disease Control: Penicillinase-producing *Neisseria gonorrhoeae*. *Mordidity Mortality Weekly Rep* 28:85-87, 1979.

3. Rendin RW, Bourgeois AL, Lin FL: Penicillinase-producing *Neisseria gonorrhoeae* in a

prepubertal female. *J Pediatr* 94:431-432, 1979.

4. Center for Disease Control: Gonorrhea: CDC recommended treatment schedules, 1979. *Morbidity Mortality Weekly Rep* 28:13-21, 1979.

5. Willcox RR: Trobicin (Actinospectacin): A new injectable antibiotic in the treatment of gonorrhea. *Br J Vener Dis* 38:150-153, 1962.

6. Duncan LW, Holder WR, Roberts DP, et al: Treatment of gonorrhea with spectinomycin hydrochloride: Comparison with standard penicillin schedules. *Antimicrob Agents Chemother* 1:210-214, 1972.

7. Pederson AHB, Weisner PJ, Holmes KK, et al: Spectinomycin and penicillin G in the treatment of gonorrhea. *JAMA* 220:205-208, 1972.

8. Mitchell RW, Robson HG: Single-dose treatment of gonococcal ureturitis in males: Evaluation of procaine penicillin, ampicillin, and spectinomycin. *Can Med Assoc J* 110:165-167, 1974.

9. Brown J, Tabert O, Hanna JD, et al: Treatment of gonorrheal ureturitis with spectinomycin hydrochloride. *Can Med Assoc J* 110:173-176, 1974.

10. Duanćić A, Fiumara NJ, Alpert S, et al: Comparison of spectinomycin hydrochloride and aqueous procaine penicillin G in the treatment of uncomplicated gonorrhea. *Antimicrob Agents Chemother* 6:512-515, 1974.

11. Judson FN, Allaman J, Dans PE: Treatment of gonorrhea: Comparison of penicillin G procaine, doxycycline, spectinomycin and ampicillin. *JAMA* 230:705-708, 1974.

12. Kousa M, Lassus A, Järueläinen R, et al: Spectinomycin hydrochloride in the treatment of uncomplicated gonorrhea in males and females. *Br J Vener Dis* 50:291-293, 1974.

13. Karney WK, Pedersen AHB, Nelson M, et al: Spectinomycin versus tetracycline for the treatment of gonorrhea. *N Engl J Med* 296:889-894, 1977.

14. Wentworth BB, Alexander ER: Isolation of *Chlamydia trachomatis* by use of 5-iodo-2-deoxyuridine-treated cells. *Appl Microbiol* 27:912-916, 1974.

15. Jorgensen JG, Lee JC, Alexander GA: Rapid penicillinase paper strip test for detection of beta-lactamase-producing *Haemophilus influenzae* and *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 11:1087-1088, 1977.

16. Rettig PJ, Hieber JP, Nelson JD: Postgonococcal chlamydial infection in prepubertal children, abstracted. *Soc Pediatr Res* 13:466, 1979.

17. Arya OP, Rees E, Percival A, et al: Epidemiology and treatment of gonorrhea caused by penicillinase-producing strains in Liverpool. *Br J Vener Dis* 54:28-35, 1978.

18. Siegel MS, Thornsberry C, Weisner PJ: Penicillinase-producing *Neisseria gonorrhoeae:* Results of surveillance in the United States, in Siegenthaler W, Lüthy R (eds): *Proceedings of the Tenth International Conference on Chemotherapy*. Washington, DC, American Society for Microbiology, 1978, vol 1, pp 192-194.

19. Nelson JD, Mohs E, Dajani AS, et al: Gonorrhea in preschool- and school-aged children. Report of the Prepubertal Gonorrhea Cooperative Study Group. *JAMA* 236:1359-1364, 1976.

20. Branch G, Paxton R: A study of gonococcal infections among infants and children. *Public Health Rep* 80:347-352, 1965.

21. Porter IA, Wood WJ: Spectinomycin: Minimum inhibitory concentrations for *Neisseria gonorrhoeae*. *Br J Vener Dis* 50:239-240, 1974.

22. Jaffe HW, Biddle JW, Thornsberry C, et al: National Gonorrhea Therapy Monitoring Study: In vitro antibiotic susceptibility and its correlation with treatment results. *N Engl J Med* 294:5-9, 1976.

23. Thornsberry C, Biddle JW, Perine PL, et al: Susceptibility of *Neisseria gonorrhoeae* from the United States and the Far East (β-lactamase negative and positive) to antimicrobial agents, in Brooks GF, Botschlich EC, Holmes KK, et al (eds): *Immunobiology of Neisseria gonorrhoeae*. Washington, DC, American Society for Microbiology, 1978, pp 62-67.

24. Reyn A, Schmidt H, Trier M, et al: Spectinomycin hydrochloride (Trobicin) in the treatment of gonorrhea: Observation of resistant strains of *Neisseria gonorrhoeae*. *Br J Vener Dis* 49:54-59, 1973.

25. Thornsberry C, Jaffe H, Brown ST, et al: Spectinomycin-resistant *Neisseria gonorrhoeae*. *JAMA* 237:2405-2406, 1977.

26. Brownlow WJ, Watko LP, Aucoin EJ, et al: Treatment of gonorrhoea contracted in Western Pacific Region. *Br J Vener Dis* 50:113-116, 1974.

27. Oriel JD, Ridgway GL, Tchamouroff S, et al: Spectinomycin hydrochloride in the treatment of gonorrhoea: Its effect on associated *Chlamydia trachomatis* infections. *Br J Vener Dis* 53:226-229, 1977.

28. Washington JA, Yu PKW: In vitro antibacterial activity of spectinomycin. *Antimicrob Agents Chemother* 2:427-430, 1972.

29. Wagner IG, Novak E, Leslie LG, et al: Absorption, distribution and elimination of spectinomycin dihydrochloride in man. *Int J Clin Pharmacol* 1:261-285, 1968.

30. Barry JM, Koch R: Actinospectacin serum levels and clinical data, in Sylvester JC (ed): *Antimicrobial Agents and Chemotherapy—1962*. Washington, DC, American Society for Microbiology, 1963, pp 538-542.

31. McCormack WM, Finland M: Spectinomycin. *Ann Intern Med* 84:712-716, 1976.

CORRECTION

Order of Authors' Names in Signature Incorrect.—In the article titled "Craniosynostosis-Radial Aplasia: Baller-Gerold Syndrome," published in the December JOURNAL (133:1279-1280, 1979) the order of the authors' names in the signature was incorrect. The order of the authors' names should be as follows: Susan L. Sklower, MD, Judith P. Willner, MD, M. Michael Cohen, DMD, Murray Feingold, MD, Robert J. Desnick, PhD, MD.

The Role of Respiratory Infection in Intrathoracic Petechiae

Implications for Sudden Infant Death

Warren G. Guntheroth, MD; Isamu Kawabori, MD; Donald G. Breazeale; Leland E. Garlinghouse, Jr, MS; Gerald L. Van Hoosier, Jr, DVM

• Intrathoracic petechiae are characteristic of the postmortem changes found in sudden infant death syndrome. The presence and distribution of these petechiae have been claimed as evidence for airway obstruction as the mechanism of death. In a group of young, mature rats that were free of infection, hypoxic asphyxia produced an insignificant number of petechiae, whereas in all littermates infected with an enzootic virus (Sendai) large numbers of petechiae with hypoxic asphyxia developed. Rats similarly infected, but killed with an overdose of pentobarbital sodium, had no petechiae. Most importantly, infected rats with unremitting airway obstruction were free of petechiae. Thus, the experimental conditions necessary for the presence of intrathoracic petechiae are profound hypoxia and infection, with persistent circulation and respiratory effort; persistent airway obstruction does not produce petechiae, with or without infection.

(Am J Dis Child **134:364-366, 1980)**

Sudden infant death syndrome (SIDS) is diagnosed in infants who die unexpectedly between the ages of 1 to 6 months and in whom inherently lethal pathology has been excluded. The disorder is the most frequent cause of death in that age group. There are some characteristic autopsy lesions, particularly intrathoracic petechiae and pulmonary edema. Handforth,[1] after producing petechiae in rats by airway obstruction, postulated that the petechiae were due to airway occlusion by laryngospasm. Beckwith[2,3] argued that the limited distribution of the intrathoracic petechiae establishes airway occlusion as the important factor.

We were surprised to find, after recreating Handforth's experiments,[4] that unremitting airway occlusion produced petechiae in only 7% of the rats, whereas death due to breathing 100% nitrogen produced petechiae in 80% to 87% (without and with anesthesia, respectively). These rats were all "retired breeder rats," 1 year of age or older. Subsequently, we attempted to identify the vascular source of the petechial hemorrhages, using our previously successful routine of hypoxic asphyxia. Unexpectedly, we could not produce petechiae by this method. Careful scrutiny showed that the only obvious difference between the earlier group of rats and the current ones that did not demonstrate petechiae, was in age: the new "resistant" rats were mature, but less than 3 months of age. The incidence and severity of enzootic infections increase with age in rats raised conventionally in large colonies; although some of the infections represent acute viral disease, chronic mycoplasma respiratory infection is progressive in its severity with increasing age.[5] Therefore, we decided to find out whether the presence of a respiratory infection was the crucial condition in the varying prevalence of petechiae. This relationship has major significance in the human cases of SIDS, since the majority of the infants are known to have mild upper respiratory infections (URIs),

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with viral isolates obtained from 38% of the victims, and inflammation of the pharynx in more than 90%.[6]

MATERIALS AND METHODS

Twenty-four pathogen-free Sprague-Dawley rats (CD-CRL: DOBS CS [SD] BR), weighing 180 to 200 g, 45 to 60 days of age, 12 male and 12 female, were placed in cages isolated from other rats. Blood samples were obtained from each animal, and the antibody titers to Sendai virus were less than 1:10 by the hemagglutination inhibition test (HAI), which indicated no prior exposure to that virus. They were then separated into two groups of 12, with equal sex distribution. The experimental group A was inoculated with a stock virus, parainfluenza 1 (Sendai) ATCC VR 105. The inoculum was obtained by propagating stock virus in 10-day-old embryonating chick eggs, harvested after 48 hours, clarified by centrifugation, and stored at −70 °C. Median egg infectious dose for the virus was greater than 10^8, and the hemagglutination titer was 1,028. The virus was diluted 1:10 in sterile phosphate-buffered saline solution. Each experimental animal was lightly anesthetized with ether, and 0.05 mL of the Sendai dilution was instilled intranasally with a disposable microtiter pipette. The control rats, group B, were treated similarly, except that the diluted virus was inactivated.

Six days later, both groups of rats (12 with the live virus and 12 with the killed virus) were individually placed in 3-L jars that contained 100% nitrogen. Respiration usually ceased after one minute. Gasping commonly occurred one minute later, and all respiratory and cardiac activity had ceased by five minutes from the time of placement in the jar. The rat was removed from the jar, and the chest and abdomen were opened and the thoracic contents were removed en bloc. A direct, close-up photograph of the anterior aspect of the lungs was obtained immediately. Identifying data were placed on the back of the print. These photographs were then graded 0 to 4+ for the presence or absence of petechiae, without knowledge of the treatment group (Table). A score of 4+ was assigned for massive, bilateral, confluent petechiae; 1+ for one or two small petechiae in only one lung; 2+ for bilateral, but few and small petechiae; and 3+ for bilateral, numerous, but discrete lesions. We used a nonparametric test for comparison, the Wilcoxon two-sample test.

Ten additional rats similar in all respects to those in groups A and B were infected with the Sendai virus, and after six days were killed with pentobarbital sodium (40 mg) injected intraperitoneally (group C). These animals died of abrupt respiratory arrest, without gasping. A final group (D) of 12 rats identical in age, size, and sex as the other three groups were infected with the Sendai virus. After six days, they were anesthetized lightly with pentobarbital (3 mg/100 mg of body weight), the trachea was surgically exposed, and permanently occluded by cross-clamping.

Percentage of Rats With 2 to 4+ Petechiae

	Results, % (No.)		
	Present Study*		1973 Study†
Without respiratory infection, hypoxic asphyxia	Group B	0 (11)	. . .
With respiratory infection			
Hypoxic asphyxia	Group A	100 (12)	87 (15)
Pentobarbital sodium apnea	Group C	0 (10)	. . .
Airway occlusion	Group D	0 (12)	7 (15)
Cardiac arrest	. . .		27 (15)
Succinylcholine chloride apnea	. . .		20 (15)

*Data from this report on young, mature rats. Infection with acute, Sendai virus.
†Data from 1973 report.[4] Chronic mycoplasma infection assumed in these "retired breeder" rats.[5]

RESULTS

Three of the 12 control animals, group B, without infection and dead of hypoxia, had 1+ petechiae; nine had none. Of the 12 animals in group A exposed to live Sendai virus, one animal died prior to the hypoxic exposure; the other 11 all demonstrated bilateral petechiae when killed by hypoxia. Six had 2+ petechiae, three had 3+, and two had 4+ ($P < .01$).

One of the ten animals in group C, infected and killed by abrupt respiratory arrest with pentobarbital, had 1+ petechiae (no significant difference from the control group). In group D, infected and killed by airway obstruction one of 12 had 1+ petechiae (again, not significantly different from the control group). None of the rats from any of the four groups had petechiae on the ventral surfaces of the abdominal viscera.

COMMENT

We have combined the data from the four groups comprising this report with those of our earlier experiments in rats.[4] To summarize the factors demonstrated to produce petechiae, we have used the earlier method of presenting the results, grouping 0 to 1+ as negative and 2 to 4+ as positive. In young, uninfected animals, petechiae were rarely seen, even with hypoxic asphyxia, whereas the combination caused petechiae in all of the animals. On the other hand, infection was not sufficient to produce petechiae in the absence of respiratory effort (overdose of pentobarbital or succinylcholine chloride) nor with airway occlusion. Abrupt cardiac arrest, produced by administration of intracardiac potassium chloride, was earlier found to produce petechiae in only four of 15 rats (27%), which suggests that persistence of circulation during hypoxia facilitated the development of petechiae. Thus, common factors that are required to produce intrathoracic petechiae are infection and hypoxia, with respiratory movement and intact circulation.

Most striking is the failure of airway obstruction to produce petechiae, with or without infection. Handforth[1] and Beckwith[2] pointed out that the petechiae are intrathoracic in SIDS, and not on abdominal viscera. They deduced that negative pressure within the thorax was causally related, presumably by increasing the transmural pressure in the pulmonary blood vessels, causing rupture. However, the pulmonary vessels are completely within the thorax, and the drop in pressure with a deep inspiratory effort is directly transmitted to those vessels.

There are examples from forensic pathology that agree with our findings of no petechiae with airway occlusion. Marshall[7] reported that petechiae were infrequent in asphyxiation cases due to plastic bags or aspirated foreign bodies, and Camps[8] stated that abrupt death by hanging

caused no petechiae. Examining for airway obstruction by postmortem roentgenography, we found only two victims of SIDS without a clear airway, out of 78.[9] A group of autopsy cases of infants dying of other causes showed one of 22 without a definite airway.

Sendai virus is a common pathogen in rats, and produces an acute respiratory infection, rarely lethal, similar to a human URI. Considering that most human infants dying with SIDS have URIs, which are not lethal for the healthy human, the parallel between the Sendai virus and the human viruses seems reasonable. A nonlethal virus may cause petechiae when the infection coincides with a lethal stress. In our rat model, the lethal factor was hypoxia, (with vigorous respiratory movements and an intact circulation) and postmortem evidence from human cases favors the same factor, hypoxia, in SIDS.[10] Although Naeye's evidence suggests chronic hypoxia, the acute episode resulting in death appears to be apnea, usually sleep apnea. Beginning with Steinschneider's in-hospital observations,[11] many centers have now observed infants with recurrent episodes of apnea, who require resuscitation.[12] Some of these patients have subsequently died and had autopsy findings consistent with SIDS. The majority of the observed or recorded apneic episodes are not obstructive, but central, based on the absence of respiratory effort.

Although viral respiratory infections are not usually lethal, and certainly small petechiae are not, the very high prevalence of URIs in SIDS victims suggests that URIs contribute in some way. The URIs seem to increase the frequency of prolonged apnea.[11] One mechanism that has been suggested is that the URI interferes with the infant's sleep, and sleep deprivation increases the chance of failure to arouse from sleep apnea in kittens.[13]

If sleep apnea leads to SIDS, which is associated with intrathoracic petechiae, the absence of petechiae in our experiments with apnea produced by pentobarbital or succinylcholine may seem to be in conflict. However, sleep apnea is a primary apnea, such as the apnea of the dive reflex[14]; primary apnea is usually followed by either arousal or hypoxic apnea. In animal experiments, hypoxic apnea is followed by gasping,[15] whereas gasping is suppressed by pentobarbital or succinylcholine. When not suppressed by drugs, gasping is usually effective in autoresuscitation in rats and in the newborn human; gasping may remain effective for the first three or four weeks in human infants and could account for the sparing of the first month of life by SIDS. If recurrent episodes of apnea and gasping occurred, the pathologic changes found by Naeye[10] in victims of SIDS could be accounted for, including petechiae.

In conclusion, we find that the causes of the intrathoracic petechiae in rats are multifactorial: infection and hypoxia, with persistent respiration and circulation. Persistent airway obstruction does not produce petechiae, with or without infection.

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References

1. Handforth CP: Sudden unexpected death in infants. *Can Med Assoc J* 80:872-873, 1959.

2. Beckwith JB: Observations on the pathological anatomy of the sudden infant death syndrome, in Bergman AB, Beckwith JB, Ray CG (eds): *Sudden Infant Death Syndrome*. Seattle, University of Washington Press, 1970, pp 83-132.

3. Beckwith JB: The sudden infant death syndrome: A new theory. *Pediatrics* 55:583-584, 1975.

4. Guntheroth WG: The significance of pulmonary petechiae in crib death. *Pediatrics* 52:601-603, 1973.

5. Lindsey JR, Baker HJ, Overcash RG, et al: Murine chronic respiratory disease. *Am J Pathol* 64:675-705, 1971.

6. Bergman AB, Ray CG, Pomeroy MA, et al: Studies of the sudden infant death syndrome in King County, Washington: III. Epidemiology. *Pediatrics* 49:860-870, 1972.

7. Marshall TK: Significance of petechiae, in Bergman AB, Beckwith JB, Ray CG, (eds): *Sudden Infant Death Syndrome*. Seattle, University of Washington Press, 1970, p 122.

8. Camps FE: Discussion, in Camps FE, Carpenter RG (eds): *Sudden and Unexpected Deaths in Infancy (Cot Deaths)*. Bristol, England, John Wright & Sons, 1972, p 71.

9. French JW, Beckwith JB, Graham CB, et al: Lack of postmortem radiographic evidence of nasopharyngeal obstruction in sudden infant death syndrome. *J Pediatr* 81:1145-1148, 1972.

10. Naeye RL: Hypoxemia and the sudden infant death syndrome. *Science* 186:837-841, 1972.

11. Steinschneider A: Prolonged apnea and the sudden infant death syndrome: Clinical and laboratory observations. *Pediatrics* 50:646-654, 1972.

12. Kelly DH, Shannon DC, O'Connell K: Care of infants with near miss sudden infant death syndrome. *Pediatrics* 61:511-514, 1978.

13. McGinty DJ, Harper RM: Sleep physiology and SIDS: Animal and human studies, in Robinson RR (ed): *SIDS 1974*. Toronto, Canadian Foundation for the Study of Infant Deaths, 1974, p 201.

14. French JW, Morgan BC, Guntheroth WG: Infant monkeys: A model for crib death. *Am J Dis Child* 123:480-484, 1972.

15. Guntheroth WG, Kawabori I: Hypoxic apnea and gasping. *J Clin Invest* 56:1371-1377, 1975

Esophageal Perforations in Premature Infants and Comments on the Diagnosis

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• **Traumatic perforation of the esophagus follows oropharyngeal suctioning or endotracheal intubation. The diagnosis frequently is made from a routine chest roentgenogram that shows a nasogastric tube in the right pleural space with or without a pneumothorax. The lesion is seen most often in infants of low birth weight.**

(*Am J Dis Child* 134:367-368, 1980)

In the reported cases[1-7] of complete perforation of the esophagus, the authors have noted the traumatic cause of the lesion and discussed the aspects of diagnosis and treatment.

See p 417.

None of the reports have emphasized that perforation of the right parietal pleura and a right pneumothorax are findings that frequently lead to the diagnosis of the esophageal lesion. This observation was made after our experiences with esophageal perforations in five premature infants. This event provides an important clue in the diagnosis.

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SUBJECTS AND METHODS

Diagnosis of esophageal perforation was made in five of 1,700 infants who were admitted to three regional neonatal intensive care centers. The clinical features of these five cases are summarized in the Table. All the infants had a low birth weight and were premature by gestational age. Four of the five infants were ventilated mechanically when the diagnosis of perforation was made. In one of the five infants, the esophageal perforations were not identified until the time of autopsy, even though mediastinitis had been noted two days prior to death during surgical ligation of a patent ductus arteriosus. In that case, one perforation was seen in the posterior esophagus above the carina of the trachea and a second was seen in the esophagus below the carina. The medial portion of the right parietal pleura was intact.

In the four remaining cases, the diagnosis was made primarily by a chest roentgenogram. A right pneumothorax was present in all four cases. In infants 1, 3, and 5, a nasogastric tube was seen in the right pleural space at the time that the pneumothorax was identified on the chest roentgenogram. In infants 1, 2, and 3, a "milky drainage" followed feedings and was collected from the right pleural cavity via chest tube or thoracotomy hole.

All the infants were treated conservatively with medical management, including antibiotics. There were three deaths. Two resulted from causes that related to the presence of esophageal injury, namely sepsis and respiratory failure.

COMMENT

The salient features of 17 reported cases of traumatic perforation of the esophagus are as follows. Of the 17 infants studied, 14 weighed less than 2,500 g. The frequency with which esophageal perforations occur in low birth weight infants probably relates to the fact that these infants often have pulmonary disease and require intubation and oropharyngeal suctioning, or require frequent, intermittent gavage feedings by nasogastric tube.

In the majority of cases, the diagnosis was made with a chest roentgenogram during the first ten days after birth. In 11 of 17 cases, a nasogastric tube was seen to lie in the right pleural space, and in nine of these there was an accompanying right pneumothorax. Although Kassner et al[3] have noted the clinically "silent" nature of this lesion, in our experiences pneumothoraces and milky drainage from a chest tube are clinical signs that cause alarm.

The involvement of the right pleural space and complete perforations of the esophagus seem unique and may have an anatomical basis. As it descends in the posterior mediastinum, the esophagus contacts the right parietal pleura just below the bifurcation of the trachea,[9,10] and then swings to the left a few centimeters above the diaphragm to contact the left parietal pleura and brace against the descending aorta. It is our hypothesis that the rightward deviation of the esophagus and inadequate extramural support of its right side wall predisposes the

Esophageal Perforations

Infant	Sex	Gestation, wk	Birth Weight, g	Intubate/ Suction	Age	Diagnosis, Roentgenogram	Outcome
1	F	30	1,964	+	10 Days	Aberrant nasogastric tube, right pneumothorax	Died at 8 mo, bronchopulmonary dysplasia
2	M	30	2,040	+	5 Days	Right pneumothorax	Survived
3	F	32	1,570	+	6 Days	Aberrant nasogastric tube, right pneumothorax	Survived
4	M	29	1,100	+	7 Days*	. . .	Died, sepsis
5	F	29	850	+	< 6 hr	Aberrant nasogastric tube, right pneumothorax	Died, 43 hr, from respiratory failure

*At autopsy.

right parietal pleura to perforation by a stiff suction catheter or an endotracheal tube with a stylet. Unfortunately, the autopsy findings in infant 4 do not support this hypothesis. However, this is one case in which the right parietal pleura was not involved.

We also have some doubt about the spontaneity of so-called "spontaneous" esophageal perforations,[8] since a right pneumothorax was present in 11 of the 13 reported cases. The predilection for the right side in these cases leads us to speculate that suctioning at birth may have been an underlying trauma and possible cause.

We remind those who intubate and suction newborn infants, particularly infants with low birth weight, to exercise care in placing a stylet within an endotracheal tube and to note carefully the position of the head and neck during intubation. The airway is most patent when the neck is horizontal to the table.[11] Hyperextension of the neck may play a role in the genesis of esophageal tears, particularly when a stiffened catheter or endotracheal tube is introduced into the oropharynx. The frequency with which esophageal injury occurs may relate inversely to the experience of the person performing the intubation or suctioning.

In summary, esophageal perforations are rare, especially when one considers the number of infants who are suctioned and intubated without incident every day. When perforations occur, however, they frequently are heralded by roentgenographic findings of a nasogastric tube lying free in the right pleural space together with a right pneumothorax. These signs are important clues to the diagnosis of complete perforation of the esophagus.

References

1. Lee SL, Kuhn JP: Esophageal perforation in the neonate: A review of the literature. *Am J Dis Child* 130:325-329, 1976.
2. Touloukian RH, Beardsley GP, Ablow RC, et al: Traumatic perforation of the pharynx in the newborn. *Pediatrics* 59:1019-1022, 1977.
3. Kassner EG, Baumstark A, Balsam D, et al: Passage of feeding catheters into the pleural space: A radiographic sign of trauma to the pharynx and esophagus in the newborn. *Am J Roentgenol* 128:19-22, 1977.
4. Ducharme JC, Bertrand R, Debie J: Perforation of the pharynx in the newborn: A condition mimicking esophageal atresia. *Can Med Assoc J* 104:784-787, 1971.
5. Khanna NN, Wijesekera S, Suckmore FN, et al: Esophageal rupture in a premature infant. *J Pediatr* 92:641-642, 1978.
6. Warden HD, Mucha SS: Esophageal perforation due to trauma in the newborn. *Arch Surg* 83:813-814, 1961.
7. Kanarek KS, David RF: Traumatic perforation of the esophagus in a newborn. *J Florida Med Assoc* 66:288-289, 1979.
8. Aaronson IA, Cynes S, Louw JH: Spontaneous esophageal rupture in the newborn. *J Pediatr Surg* 10:459-465, 1975.
9. Payne WS, Olsen Am: The origin, form and function of the esophagus, in Payne WS, Olsen AM (ed): *The Esophagus.* Philadelphia, Lea & Febiger, 1974, p 2.
10. Warwick R, Williams PL: The esophagus, in *Gray's Anatomy,* ed 35. Philadelphia, WB Saunders Co, 1973.
11. Gluck L: Special problems of the newborn. *Hosp Pract* 13:75-88, 1978.

Urinary Infection in Infants and Preschool Children

Five-Year Follow-up

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• A group of 1,617 infants and 1,711 preschool children were studied for symptomatic and asymptomatic urinary infection and followed up for three to five years. Asymptomatic bacteriuria was found in 1.8% of female infants, 0.5% of male infants, 0.8% of preschool girls, and none of the preschool boys. Seventeen percent of the infants and 13% of the preschool children with urinary infection studied roentgenographically had upper tract damage; 46% of the infants and 9% of the preschool children had vesicoureteral reflux. Infants with normal urinary tracts and urinary infection with or without reflux tended to have recurrent infection, whereas the kidneys remained anatomically normal. The infants with high-risk lesions, such as obstructive uropathy and vesicoureteral junction ectopia and deformity, had substantial bacteriuria on screening culture.

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It is possible to recognize the asymptomatic infant and child with significant bacteriuria.[1] The purposes of this study were: (1) to define the prevalence of asymptomatic urinary infection in infants and preschool children; (2) to determine the frequency and type of urological abnormalities associated with asymptomatic and symptomatic urinary infection; and (3) to provide five-year follow-up of the infants and preschool children with urinary infection.

SUBJECTS AND METHODS

All children (a total of 1,617 infants and 1,711 preschool children; 1,715 girls and 1,613 boys) seen between January 1970 and January 1975 in a pediatric office that serves a middle- to upper-middle-class population were studied. All children with symptomatic urinary infection (group 1) and all normal children with no symptoms of urinary infection who were tested for bacteriuria (group 2) were included. The normal children were selected from those children brought to the office for a "well-child" checkup. No parent refused the urine culture procedure as part of the well-child evaluation. The normal children (group 2) were tested at 3 to 6 months, 15 to 18 months, 3 years, and 4 years of age. Groups 1 and 2 are categorized into four subgroups: group A, urinary infection without vesicoureteral reflux or anatomical abnormality; group B, urinary infection associated with vesicoureteral reflux but no anatomical abnormality; group C, urinary infection associated with a congenital obstructive uropathy; and group D, urinary infection associated with vesicoureteral junction ectopia.

CULTURE TECHNIQUE AND IMPLICATIONS

The child's perineal area was cleaned with benzalkonium antiseptic solution applied by a trained office assistant, and the urine specimen was collected with a sterile pediatric collector or urine container. The children who did not urinate within 30 to 45 minutes had cultures taken on a subsequent visit.

Within five minutes after collection, the urine was tested for bacteriuria using the miniature culture (Testuria Kit)[2,3]; was tested for levels of protein, blood, and glucose; and was centrifuged and examined for pyuria under high-power lens. If the culture was positive (> 25 colonies indicates > 100,000 colonies/mL on standard pour plate), a second voided specimen was obtained by the technique described earlier for quantitative bacterial count by standard pour plate technique. A third urine specimen was obtained by urethral catheterization after informed consent during the last three years of the screening program.

The well child with no symptoms of urinary infection was considered to have a urinary tract infection if a colony count of greater than 100,000/mL of the same organism was obtained on the two clean voided cultures during the first two years of the study. During the last three years of the study, the well child was regarded as having a urinary infection if two

Table 1.—Radiologic Evaluation in Subjects With Urinary Infection

	Intravenous Pyelogram	Abnormal Grade Findings (Reflux)		
		Grades 1-2	Grade 3	Grade 4
Asymptomatic				
Female infants	3	4	3	2
Male Infants	1	1	0	0
Preschool girls	0	1	0	0
Preschool boys	0	0	0	0
Symptomatic				
Female Infants	4	5	4	1
Male Infants	0	0	0	0
Preschool girls	6	0	0	1
Preschool boys	0	0	0	0

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Table 2.—Five-Year Follow-up of Children With Congenital Obstructive Uropathy*

Sex/Age at Diagnosis	Initial Findings: Symptomatic (S) or Asymptomatic (A)	Initial Findings: Intravenous Pyelogram	Initial Findings: Cystourethrogram While Voiding	Initial Findings: Cystoscopy	Type of Surgery
M/3 mo	A	Advanced loss L renal cortex and hydronephrosis	Gastrointestinal bilateral reflux	Stricture membranous prostatic urethral junction	Pyelouretoplasty
F/15 mo	S	L chronic pyelonephritis, hydroureter, and hydronephrosis with duplicated L system	G4 L reflux	U-V; junction obstruction; duplicated ureters with ectopic opening	Ureteroneocystostomy
F/4 mo	A	Horseshoe kidney; blunted lower calyces, fused duplicated system L	G2 L reflux	...	...
F/14 mo	S	R pelvocaliectasis cortex thin	G3 R reflux	U-V junction; obstruction ectopic R orifice with duplication of ureters; blind ureter	Ureteroneocystostomy; excision of duplicated orifice
F/6 wk	S	Absent R kidney; L pelvocaliectasis and ureterectasis	Decreased bladder emptying	Bladder diverticulum and decreased musculature	Diverticulectomy; ureteroneocystostomies
F/2 yr	A	N	N	Prominent indentation of urethra at intermuscular incisura (dilation)	...
F/3 yr	S	Hydroureter; anomaly of lumbar and sacral spine (neurogenic bladder)	N	Trigone wide; ectopic patulous orifice	...
F/2½ yr	S	Nonfunctioning R kidney; severe R hydroureters and hydronephrosis	N	R ureteral obstruction	R nephroureterectomy
F/4 yr	S	N	N	Posturethral ring-like deformity (dilation)	...
F/2 yr	S	Duplication R system with chronic pyelonephritis and hydroureter	N	Duplication of ureters with ectopic opening into bladder neck	Heminephrectomy and ureteroneocystostomy

*N indicates normal; X, length of infection; G4, G3, and G2, grades 4, 3, and 2; U-V, ureterovesical.

Table 3.—Five-Year Follow-up of Children With Primary Ureterovesical Junction Ectopia*

Sex/Age at Diagnosis	Initial Findings: Symptomatic (S) or Asymptomatic (A)	Initial Findings: Intravenous Pyelogram	Initial Findings: Cystourethrogram While Voiding	Initial Findings: Cystoscopy	Type of Surgery	Five-Year Follow-up: Intravenous Pyelogram	Five-Year Follow-up: Cystourethrogram While Voiding	Five-Year Follow-up: Recurrent Infection <1 yr	Recurrent Infection 1-3 yr	Recurrent Infection >3 yr
F/12 mo	A	N	G3 reflux	U-V junction ectopia	...	...	...	Lost	...	...
F/12 mo	A	R pelvocaliectasis	G1 reflux	U-V junction ectopia	...	N	N	...	X	...
F/18 mo	S	N	G3 reflux	U-V junction ectopia	...	N	N	...	X	...
F/4 mo	A	N	G3 reflux	R U-V junction ectopia and deformity	Ureteroneocystostomy	N	N	X	...	...
F/18 mo	S	L pelvocaliectasis	G3 reflux	U-V junction ectopia	...	N	N	...	X	...
F/7 mo	S	N	G3 reflux	U-V junction ectopia	...	N	N	...	...	X

*N indicates normal; G3 and G1, grades 3 and 1; U-V, ureterovesical; X, length of infection.

clean voided cultures showing greater than 100,000 colonies/mL of the same organism plus substantial bacteriuria by urethral catheterization were obtained. The sick child with symptoms of urinary infection was considered infected if one or two urine cultures had greater than 100,000 colonies/mL.

Children with positive cultures as just defined were placed on a regimen for two to three weeks of sulfisoxazole acetyl, ampicillin sodium, or the antibiotic indicated on culture sensitivities. An intravenous pyelogram (IVP) and cystourethrogram made while voiding (VCU) were obtained after the treatment was completed.

The IVP was considered abnormal if there was (1) local parenchymal loss; (2) calyceal distortion and dilation;

Five-Year Follow-up				
		Recurrent Infection		
Intravenous Pyelogram	Cystourethogram While Voiding	< 1 yr	1-3 yr	> 3 yr
R kidney normal	N	...	...	X
N	N	X	...	...
N	N	...	X	...
Improved	N	...	...	X
N	N	...	X	...
N	N	X	...	...
No change	N	...	...	X
N	N	X	...	...
N	N	X	...	...
N	N	...	X	...

and (3) dilation of the ureters. The following roentgenographic grading of the vesicoureteral reflux was used: grade 1, minimal reflux into lower ureter; grade 2, entire ureter filled; grade 3, upper urinary tract filled; grade 4, grade 3 plus severe distention of the renal pelvis and calyces.

Those children with abnormal roentgenographic findings, inability to clear the initial infection with one or more courses of therapy, or repeated infection had consultation and cystoscopy by a urologist. The children with recurrent infection were placed on a program consisting of nitrofurantoin (25 to 50 mg at night from six weeks to one year, depending on the size of the child and recurrent rate of infection) and increased fluid intake. These children were subsequently followed up with urinalysis, urine cultures, roentgenography, and surgery when indicated by the urologist in communication with the pediatrician. Those children with urinary infection and normal roentgenograms were subsequently followed up by the pediatrician.

RESULTS

Substantial asymptomatic bacteriuria occurred in 15/420 (3.6%) of the female infants (< 1 year 11 months old) and 7/391 (1.8%) of the male infants. It occurred in 7/375 (1.9%) of the preschool (< 4 years 11 months old) girls and 0/285 of the preschool boys. These figures are based on two clean catch urine cultures obtained during the first two years of the study. After the addition of urethral catheterization during the last three years of the study, asymptomatic bacteriuria occurred in 7/390 (1.8%) of the female infants and 2/416 (0.5%) of the male infants and also in 4/530 (0.8%) of the preschool girls and 0/521 of the preschool boys. However, this decrease was not statistically significant in any of the groups. Urinary infection was diagnosed in 42 children younger than 1 year of age, in 17 between 1 and 2 years, and in 44 between 2 and 5 years of age. The organisms present in the infants were *Escherichia coli* (55%), *Proteus* (22%), *Staphylococcus aureus* (11%), and *Pseudomonas* (11%). *Escherichia coli* was present in all of the preschool children.

Between January 1970 and January 1975, 25 female infants, three male infants, 28 preschool girls, and four preschool boys were recognized as having symptomatic urinary infection during visits to the office because of sickness. The prevalence of symptomatic urinary infection is unknown.

Table 1 gives the results of roentgenographic evaluation of the infants and children with asymptomatic and symptomatic urinary infection. Eight of the 47 infants whose conditions were studied by IVP had upper tract damage. Ten of the 43 infants with conditions studied by VCU had grades 1 to 2 vesicoureteral reflux, seven had grade 3, and three had grade 4. Six of the 31 preschool cases studied by IVP showed upper tract damage; one of the 27 studied by VCU was grade 1 to 2 vesicoureteral reflux, and one was grade 4.

There was 52 children (group A) who had urinary infection without vesicoureteral reflux or anatomical abnormalities. All initial IVPs and VCUs were normal. Recurrent infection occurred during the next three years.

Ten children (group B), all female, with normal urinary tracts had urinary infection associated with vesicoureteral reflux. Five had grade 3 and/or 4 reflux. Four of the nine followed up continued to have recurrent infection for the next three to five years. During the five-year follow-up of groups A and B, urine cultures were obtained at one- to two-month intervals for the first six months and then approximately at six-month intervals, after diagnosis of the urinary infection.

Table 2 gives the initial findings and five-year follow-up data for each child with congenital obstructive urinary tract abnormalities (group C) and Table 3 gives the findings for those with vesicoureteral junction

ectopia and deformity (group D). Ten (five infants and five preschool children) (group C) of the 78 (13%) who underwent roentgenographic studies had congenital obstructive urinary tract anomalies with reflux. Six (all infants) (group D) of the 78 (7.5%) whose conditions were studied roentgenographically had primary vesicoureteral reflux associated with vesicoureteral junction ectopia and/or deformity.

Twenty-four children, 22 female and two male, with symptomatic or asymptomatic bacteriuria had no initial IVP or VCU. The parents refused permission or the children were lost to follow-up. Of the 12 followed up one to three years, none had further infection.

COMMENT

The reduction in the number of urinary infections diagnosed by the addition of urethral catheterization to two clean catch cultures ("Results" section) was not statistically significant. However, the clean catch group was studied prior to the urethral catheterization group. Studies by Pryles et al[4] of 42 children and Redman and Bissada[5] of 200 infants showed no urinary infection secondary to a single urethral catheterization. No child in the study had a urinary infection after a single urethral catheterization. Urethral catheterization was found to be an easier, less traumatic, and more successful technique to diagnose cases of older infants and preschool children as outpatients than was suprapubic aspiration.

Vesicoureteral reflux (Table 1) was found in 46% of infants vs 9% of preschool children. Roberts and Riopelle[6] have shown in infant monkeys that vesicoureteral reflux disappears with maturity. The amount of anatomical upper tract damage (Table 1) was similar in the infants (17%) and preschool children (19%).

During the three- to five-year follow-up of group A, the 52 children who had urinary infection without associated reflux, all of whom had normal IVPs and VCUs initially, were anatomically normal. Their infections recurred primarily within the first year and stopped within three years.

In group B, of the ten children, all female, who had vesicoureteral reflux secondary to urinary infection, one child had an abnormal IVP but subsequent repeated IVP was normal. Recurrent infection was more common in group B than in group A and continued for more than three years without a change in the IVPs. Although the children with reflux had a greater number of recurrent infections for a longer period of time, urinary infection in a normal urinary tract with or without reflux had a good prognosis when there was early treatment of recurrent urinary infections.

In most instances, reflux with infection leading to pyelonephritis seems to be necessary for a kidney to have impaired growth.[7] Therefore, early diagnosis and treatment of urinary infection with follow-up should decrease the morbidity in infants and young children with rapidly growing kidneys.

Table 2 gives the follow-up of the two groups with high risk for development of chronic pyelonephritis. Group C contains ten infants and children with obstructive uropathy, eight of whom had abnormal initial IVPs. Group D contains the infants and children with vesicoureteral junction ectopia and/or deformity with grade 3 and/or 4 primary reflux and an abnormal initial IVP in 2/6. Three of ten in group C and 3/6 in group D were recognized as having asymptomatic bacteriuria when younger than 2 years of age (5/16 $<$ 12 months of age). The children with congenital obstructive uropathy (group C) who initially had symptomatic urinary infection had not been previously tested for asymptomatic bacteriuria in infancy. During the next three to five years, group C infants and children continued to have recurrent infection after surgical repair of the obstructive uropathy. However, the follow-up IVPs were abnormal in only two instead of eight. In group D, one infant had a ureterocystostomy, with no further infection. Others were treated conservatively, and all had normal IVPs three to five years later. Willscher et al[8] showed that surgery on children with primary reflux was successful in preventing recurrent postoperative infection, with a statistically significant ($P < .05$) increase in renal growth. Early diagnosis, surgical treatment, and prompt treatment of recurrent infection seemed to reduce the morbidity and mortality in these high-risk groups. An 11% mortality among infants with urinary infection has been reported.[9]

The fact that infants seen between 1970 and 1975 with obstructive uropathy and vesicoureteral junction ectopia and deformity had substantial bacteriuria suggests that such cultures can help in diagnosing these high-risk groups earlier and in possibly changing the natural history. The ten-year study of Randolph et al[10] suggests that further urinary infections can be prevented.

Ayerst Laboratories, New York, supplied the Testuria kits, and Sterilon Corp, Braintree, MA, supplied the sterile pediatric urine bags.

Richard Glassock, MD, provided criticism of the manuscript.

Nonproprietary Name and Trademarks of Drug

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*

References

1. Siegel SR, Sokoloff B, Siegel B: Asymptomatic and symptomatic urinary tract infection in infancy. *Am J Dis Child* 125:45-47, 1973.

2. Dodge WF, West EF, Fras PA, et al: Detection of bacteriuria in children. *J Pediatr* 74:107-110, 1969.

3. Hobday JB: A simplified culture method for detecting asymptomatic bacteriuria in children. *Pediatrics* 38:902-905, 1966.

4. Pryles CB, Atkin MD, Morse TS, et al: Comparative bacteriologic study of urine obtained from children by percutaneous suprapubic aspiration of the bladder and by catheter. *Pediatrics* 24:983-991, 1959.

5. Redman JF, Bissada NK: Direct bladder catheterization in infant females and young girls. *Clin Pediatr* 15:1060-1061, 1976.

6. Roberts JA, Riopelle AJ: Vesicoureteral reflux in the primate: II. Maturation of the ureterovesical junction. *Pediatrics* 59:566-568, 1977.

7. McRae CU, Shannon FT, Utley WLF: Effect on renal growth of reimplantation of refluxing ureters. *Lancet* 1:1310-1313, 1974.

8. Willscher MK, Bauer SB, Zammuto PJ: Renal growth and urinary infection following antireflux surgery in infants. *J Urol* 115:722-725, 1976.

9. Woodward JR: The urologist and the newborn, in Fishbein M (ed): *Urology.* New York, Medical World News, 1973, p 21.

10. Randolph MF, Morris KE, Gould EB: The first urinary tract infection in the female infant. *J Pediatr* 86:342-348, 1975.

Hyaline Membrane Disease

A Controlled Study of Inspiratory to Expiratory Ratio in Its Management by Ventilator

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• Sixty-nine neonates with severe hyaline membrane disease (HMD) were mechanically ventilated using either a 1:2 or a 2:1 inspiratory to expiratory (I/E) ratio. Survivors in the 2:1 group required a lower fraction of oxygen in the inspired air (FiO_2) and lower end-expiratory pressure to achieve satisfactory oxygenation. During the first week of life, time of exposure to $FiO_2 > 0.60$ while being mechanically ventilated was 29.7 ± 7.5 hours for the 1:2 group and 6.9 ± 2.7 hours for the 2:1 group, while time of exposure to end-expiratory pressure > 3 cm H_2O was 49.4 ± 7.9 hours for the 1:2 group and 13.4 ± 7.4 hours for the 2:1 group. Mortality and the incidence of air leak, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and pulmonary hemorrhage were not different for the two groups. Using an increased I/E ratio during the acute phase of HMD improved oxygenation but did not alter morbidity or mortality.

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Hyaline membrane disease (HMD) is a major cause of respiratory failure in the neonatal period. During the past decade, mechanical ventilation has become an accepted therapy for this disease. Increasing the inspiratory to expiratory (I/E) ratio is a technique that has been used to improve the oxygenation of mechanically ventilated babies.[1-6] A retrospective review[7] has suggested that increasing the I/E ratio increases the arterial partial pressure of oxygen (Pao_2) at lower peak inspiratory pressure, increases the survival rate, and reduces the incidence of bronchopulmonary dysplasia (BPD) for babies mechanically ventilated for HMD.

Although use of an increased I/E ratio has become an accepted method for improving oxygenation,[8,9] its efficacy has not been established in a prospective, controlled, clinical trial. To determine the usefulness of this technique, patients with severe HMD requiring mechanical ventilation were randomly and prospectively assigned to either a 1:2 or a 2:1 I/E ratio treatment group. We then examined the effect of this therapy on mortality, morbidity, the required fraction of oxygen in the inspired air (FiO_2), and respirator pressure settings.

PATIENTS AND METHODS

Patients

The study population consisted of all patients (n = 74), admitted to the Magee-Womens Hospital intensive care nursery in Pittsburgh during the 12-month period ending in December 1978, who required mechanical ventilation for the treatment of HMD. The diagnosis of HMD was based on the clinical findings of cyanosis, expiratory grunting, nasal flaring, intercostal retractions, and reticulogranular infiltrates on chest roentgenogram. Indications for mechanical ventilation in these patients with HMD were either (1) a $Pao_2 < 50$ mm Hg when the patient was exposed to continuous distending pressure of 8 cm H_2O and $FiO_2 > 0.80$ or (2) a pH < 7.25 that was unresponsive to other therapy or (3) apnea with frequently occurring bradycardia. Of the 74 patients admitted to the study, five were later excluded because they had a surgically induced pneumothorax at the time of patent ductus arteriosus (PDA) ligation (one in each group), evidence of air leak prior to mechanical ventilation (one in the 1:2 group), documented sepsis (one in the 1:2 group), or received tubocurarine chloride (one in the 2:1 group). Patients were prospectively matched for birth weight, sex, and place of birth (at Magee-Womens Hospital vs a referral hospital) and then randomly assigned by coin toss to either a 1:2 or 2:1 I/E ratio treatment group.

Methods

The patients were ventilated using time-cycled, pressure-limited respirators (Baby Bird respirators, Bird Corp, Palm Springs, Calif) that were initially set at an inspiratory pressure of 22 cm H_2O, an end-expiratory pressure of 3 cm H_2O, a flow rate of 10 L/min, a rate of 20 cycles per minute, and an FiO_2 sufficient to relieve cyanosis. We found that a square pressure wave was generated when the machine was adjusted in this manner. The I/E ratio and the flow rate remained constant throughout the course of mechanical ventilation as long as the ventilator rate was greater than 20 cycles per minute; at lower rates, the maximum inspiratory times were set at one and two s for the 1:2 and 2:1 groups, respectively.

The I/E ratios and inspiratory times were set using I/E ratio meters whose accuracy was checked with a stopwatch. Ventilator settings were checked for accuracy at least once an hour by inhalation therapists using an in-line pressure manometer. The settings and FiO_2 changes were adjusted to maintain the patient's Pao_2 at 45 to 60 mm Hg and the pH at 7.25 to 7.35. Alterations in inspired oxygen and/or end-expiratory pressure were made to prevent hypoxia while changes in rate (to a maximum of approximately 40 breaths per minute) and inspiratory pressure were made to prevent acidosis, hypercarbia, and hypoxia, when necessary. No attempts were made to inhibit spontaneous respirations. Patients were weaned from the ventilator using the method of Gregory.[10]

Except for ventilator management, study patients were treated according to the routines of the intensive care nursery. Babies received care in humidified, servo-controlled incubators, with heat shields for patients weighing < 1,200 g. Starting on

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the fifth day of life, babies received daily supplemental multivitamins and vitamin E (15 IU) by gavage. Fluid was administered at a rate of 65 mL/kg/day initially and subsequently adjusted depending on changes in body weight.

Data obtained for each patient included laboratory determinations of pH and blood gases as well as recordings of ventilator settings. Arterial blood was sampled from umbilical, radial, or posterior tibial artery catheters at intervals determined by the clinical staff. A pH-blood gas analyzer was used to measure the pH and the blood gases. A daily tabulation was made of all measurements of the arterial partial pressure of carbon dioxide ($PaCo_2$), the Pao_2 measurements at 6 hours of age, 24 hours of age, and every 24 hours thereafter. Hourly values of measured FiO_2, ventilator rate, and respirator pressure gauge values for inspiratory pressure and end-expiratory pressure were also recorded.

Specific forms of morbidity that were tabulated included air leak, BPD, clinically important PDA, pulmonary hemorrhage, necrotizing enterocolitis, and intraventricular hemorrhage (IVH). Air leak was defined by roentgenographic evidence of pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum without evidence of bowel perforation, or massive air embolism. A PDA was diagnosed in any patient who had the classical murmur, collapsing pulses, and a hyperdynamic precordium[11]; a PDA was considered to be clinically important when the patient was symptomatic to the degree that therapy with furosemide and/or digoxin was started. Bronchopulmonary dysplasia was defined by the persistence of signs of respiratory distress in association with the typical roentgenographic findings[12] for patients who continued to require supplemental oxygen after 1 month of age. A diagnosis of IVH was made on the basis of the clinical syndrome,[13] computerized axial tomographic (CT) findings, or postmortem examination results.

Statistical analyses were performed using the χ^2 test or two-tailed Student's t test for unpaired data; a $P < .05$ was used to define statistical significance. The protocol for this study was approved by the Research Review and Human Experimentation Committee of Magee-Womens Hospital.

Table 1.—Group Characteristics*

	All Patients		Survivors	
	1:2 Group (n = 33)	2:1 Group (n = 36)	1:2 Group (n = 21)	2:1 Group (n = 18)
Sex (m/f)	19/14	20/16	12/9	10/8
Birthweight, g	1,469 ± 104	1,434 ± 108	1,695 ± 136	1,820 ± 163
Range	710-3,480	680-3,740	1,000-3,480	890-3,740
< 1,000	8	11	2	2
1,001-1,500	13	14	7	6
1,501-2,000	6	5	6	4
> 2,000	6	6	6	6
Gestational age, wk	30.6 ± 0.5	31.1 ± 0.6	31.9 ± 0.6	32.2 ± 0.7
Inborn/outborn†	21/12	24/12	13/8	12/6
Vaginal/cesarean section	24/9	23/13	15/6	10/8
Asphyxia‡	16	16	8	5
Indication for ventilation				
Acidosis	21	22	15	12
Hypoxia	3	1	3	1
Apnea	9	13	3	5
Age at start of mechanical ventilation, hr	11.8 ± 2.5	14.9 ± 3.5	21.6 ± 6.2	15.7 ± 3.4
$AaDO_2$§ at 6 hours of life, mm Hg	300.9 ± 28.2	282.3 ± 26.0	243.9 ± 26.2	195.2 ± 19.0

*Data presented are either number of patients or mean ± SEM.
†Born at Magee-Womens Hospital/born at a referral hospital.
‡Cord pH < 7.20 or one-minute Apgar score < 5.
§$AaDO_2$ indicates alveolar to arterial oxygen gradient.

Table 2.—Ventilatory Patterns of Survivors During the First Week of Life*

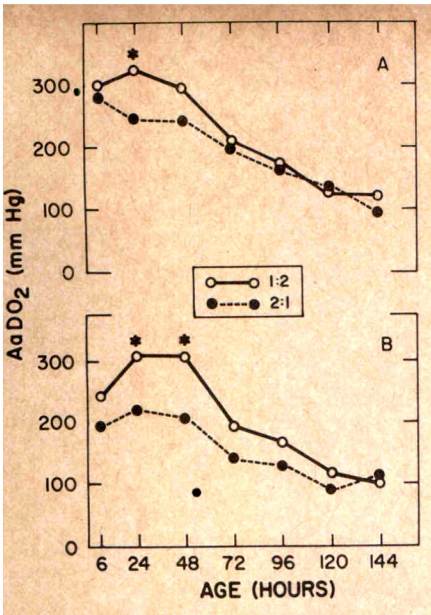
	Hours for	
	1:2 Group (n = 21)	2:1 Group (n = 18)
Total ventilation	92.8 ± 12.4	80.6 ± 14.9
Total intubation	102.7 ± 11.5	89.7 ± 15.0
Total $FiO_2 > 0.21$	149.1 ± 6.5	125.5 ± 10.1
Ventilation at		
End-expiratory pressure, cm H_2O		
> 5	8.4 ± 4.2	2.6 ± 1.9
> 4	13.9 ± 5.7	2.9 ± 2.1
> 3	49.4 ± 7.9	13.4 ± 7.4†
Inspiratory pressure, cm H_2O		
> 35	1.6 ± 1.1	0
> 30	7.0 ± 4.9	0.9 ± 0.6
> 25	18.7 ± 6.5	6.4 ± 5.1
Rate, cycles/min		
> 35	4.5 ± 1.8	4.8 ± 4.3
> 30	9.1 ± 4.7	5.1 ± 4.5
> 25	17.1 ± 7.9	13.9 ± 5.5
FiO_2		
> 0.80	7.1 ± 3.7	2.9 ± 1.1
> 0.70	17.6 ± 5.8	3.8 ± 1.8‡
> 0.60	29.7 ± 7.5	6.9 ± 2.7†
> 0.50	41.0 ± 8.4	14.9 ± 4.4†

*Mean ± SEM. FiO_2 indicates fraction of oxygen in the inspired air.
†$P < .01$.
‡$P < .05$.

RESULTS

Amongst the 69 patients who met all the study criteria, 33 were assigned to the 1:2 I/E ratio group and 36 to the 2:1 group. There were no statistically significant differences between the groups in birth factors, indications for mechanical ventilation, age at the start of mechanical ventilation, or alveolar to arterial oxygen gradient ($AaDO_2$) at 6 hours of age (Table 1). This was true when comparing survivors (patients living longer than 28 days) or all patients in each group (Table 1). We analyzed ventilator data of survivors separately to eliminate patients with extensive CNS injury secondary to IVH whose duration of mechanical ventilation was unrelated to pulmonary disease.

Survivors ventilated with the 2:1 I/E ratio required lower FiO_2 and lower end-expiratory pressure to achieve satisfactory oxygenation (Ta-



Alveolar to arterial oxygen gradient ($AaDO_2$) for (A) all patients in each group and (B) survivors in each group. Asterisk indicates statistical significance ($P < .05$): the $AaDO_2$ = ([barometric pressure —partial pressure of water vapor in saturated air] $FiO_2 - Paco_2$) $- Pao_2$.[14] FiO_2 indicates fraction of oxygen in the inspired air.

Table 3.—Peak Ventilator Settings During Entire Course of Mechanical Ventilation*

	All Patients		Survivors	
	1:2 Group (n = 33)	2:1 Group (n = 36)	1:2 Group (n = 21)	2:1 Group (n = 18)
Peak inspiratory pressure, cm H_2O	29.7 ± 1.5	28.6 ± 1.6	26.0 ± 1.1	23.5 ± 0.9
Peak expiratory pressure, cm H_2O	4.7 ± 0.9	4.5 ± 0.3	4.6 ± 0.4	3.7 ± 0.4
Peak rate, cycles/min	30.4 ± 1.5	30.0 ± 1.5	26.2 ± 1.5	25.0 ± 2.0
Peak FiO_2	0.78 ± 0.04	0.81 ± 0.04	0.72 ± 0.05	0.68 ± 0.06

*Mean ± SEM. FiO_2 indicates fraction of oxygen in the inspired air.

Table 4.—Morbidity

	All Patients		Survivors	
	1:2 Group (n = 33)	2:1 Group (n = 36)	1:2 Group (n = 21)	2:1 Group (n = 18)
Overall*	20	25	8	7
Air leak	8	13	3	4
Pulmonary hemorrhage	3	4	1	0
Bronchopulmonary dysplasia	5	4	5	4
Necrotizing enterocolitis	0	2	0	1
Intraventricular hemorrhage	13	16	2	0
Patent ductus arteriosus	2	4	2	3

*Number of patients who suffered one or more forms of morbidity.

ble 2). These results are based on analysis of data collected during the first week of life. The duration of exposure to $FiO_2 > 0.60$ while being mechanically ventilated was significantly less for the 2:1 group during the first week (6.9 ± 2.7 hours [mean ± SEM] vs 29.7 ± 7.5 hours, $P < .01$). During this period, survivors in the 2:1 group were also exposed to fewer hours of end-expiratory pressure greater than 3 cm H_2O (13.4 ± 7.4 hours vs 49.4 ± 7.9 hours, $P < .01$). The Figure presents data showing that the $AaDO_2$ was less in the 2:1 group when either all the patients (part A) or only the survivors (part B) were examined. The $AaDO_2$ for survivors in the 2:1 group was significantly lower at both 24 hours (223 ± 33 mm Hg vs 312 ± 30 mm Hg, $P < .05$) and 48 hours of age (213 ± 31 mm Hg vs 313 ± 30 mm Hg, $P < .05$) (Figure). The $AaDO_2$ values on the other days of the first week of life were not significantly different between the groups. The Pao_2 measurements used to calculate $AaDO_2$ were those obtained at 6 hours of age, then at 24-hour intervals after birth.

We did not find significant differences in other factors related to mechanical ventilation for survivors in the two groups. Carbon dioxide excretion was not significantly affected by the I/E ratio. The average daily $Paco_2$ during the first week of life (the mean of the mean of all $Paco_2$ measurements for each day) ranged from 41.9 ± 1.3 mm Hg to 47.3 ± 1.8 mm Hg for the 1:2 group and 37.5 ± 2.5 mm Hg to 47.5 ± 1.8 mm Hg for the 2:1 group; there were no group differences in $Paco_2$ on any of the first seven days. Two ventilator settings that alter the $Paco_2$, inspiratory pressure and rate, were not significantly different for the two groups (Table 2). Total hours of mechanical ventilation, intubation, and exposure to supplemental oxygen during the first week of life were not different for survivors in the groups (Table 2). Although duration of exposure to higher FiO_2 and end-expiratory pressure was different between the groups, there were no group differences in the highest peak inspiratory pressure, highest end-expiratory pressure, highest ventilator rate, or highest FiO_2 used (Table 3).

Overall morbidity was not significantly different between the groups (Table 4), nor were there differences in the occurrence of the specific forms of morbidity. Four patients in each group had pulmonary interstitial emphysema; six patients in the 1:2 group and ten in the 2:1 group each had a pneumothorax; one patient in each group had a pneumopericardium; one patient in each group had a pneumoperitoneum; and one patient in the 2:1 group had a massive air embolism. Many of these patients experienced more than one of these forms of air leak. All surviving patients with clinically significant PDA were successfully managed with medical therapy. Two survivors had IVH diagnosed by CT. Surviving patients had their maximal requirement for ventilator support during the first week of life. There were 11 survivors (seven in the 1:2 group and four in the 2:1 group) who continued to require mechanical ventilation after seven days of age. All of these patients had either air leak, PDA, pulmonary hemorrhage, or BPD. Peak inspiratory pressure used for these patients after the first week of life was 19.1 ± 1.2 cm H_2O and peak FiO_2 was 0.48 ± 0.08. Only one survivor, who was being treated for a pulmonary hemorrhage, required higher ventilator pressures in the second week than he did during the first week of life.

There were also no significant dif-

ferences in mortality between the groups. Twelve of the patients (36.4%) in the 1:2 group and 18 (50.0%) in the 2:1 group died in the first 28 days ($P > .20$). Although the proportion of infants less than 1,500 g was equal in both groups, the numerically greater mortality in the 2:1 group does occur in these low-birth-weight infants. The primary causes of death were IVH (11 cases in the 1:2 group and 15 in the 2:1 group) and air leak (one and three cases, respectively). One of the three cases in the 2:1 group whose death was clinically attributed to air leak also had an IVH diagnosed at autopsy. The diagnosis of IVH was made on clinical grounds in eight cases and at autopsy in 19. There were two deaths among "survivors" after 1 month of age, one in each group; one of these babies died at 5 months of BPD, and the other died at 6 months of nephrosis and BPD.

COMMENT

The results of our prospective study indicate that increasing the I/E ratio for babies with HMD who are mechanically ventilated improves oxygenation. Patients in the 2:1 group were adequately oxygenated at a lower FiO_2 and end-expiratory pressure during the first week of life. The improvement in oxygenation was most notable early in the course as shown by the significantly lower $AaDO_2$ for the 2:1 group at 24 and 48 hours of age. Inspiratory pressure, ventilator rate, and $Paco_2$ were not significantly different between the groups, suggesting that minute ventilation was not significantly influenced by the I/E ratios that we used.

An early study of I/E ratio[1] noted a significant decrease in right-to-left shunting, an increase in Pao_2, and no change in $Paco_2$ when the I/E ratio was increased from 1:2 to 4:1. This work was confirmed by a later study[2] that also suggested that continuous distending pressure acts synergistically with an increase in the I/E ratio to improve oxygenation. It has been suggested[2-6] that increasing the I/E ratio improves oxygenation through its effect on mean airway pressure. Although the exact mechanism is yet to be completely determined, the favorable action of increased I/E ratios on right-to-left shunting seems well established when using ventilators that generate square pressure waves.[4-6]

Despite the improvement in oxygenation associated with the increased I/E ratio during the first week of life, we did not find differences in morbidity between the groups. From their retrospective review, Reynolds and Taghizadeh[7] concluded that increasing the I/E ratio reduced morbidity by decreasing the incidence of BPD. We did not find a decreased incidence of BPD in our high I/E ratio group. This discrepancy in results may be due to the fact that we prospectively controlled for the use of end-expiratory pressure and the indications for mechanical ventilation while at the time of Reynolds and Taghizadeh's study[7] it was not possible to control for these variables. Concern has also been expressed[7] that the increase in mean airway pressure associated with the increased I/E ratio could have detrimental effects, especially if the high ratio were to be used after the acute phase of HMD when lung compliance improves. It has been suggested that the increased mean airway pressure could lead to air trapping and air leak or could compromise venous return and increase the risk of IVH. We did not find this to be the case. Our patients continued with their assigned I/E ratios throughout the course of mechanical ventilation, and those in the 2:1 group did not have a greater incidence of air leak or IVH.

We did not find that increasing the I/E ratio was associated with decreased mortality as reported by Reynolds and Taghizadeh.[7] The 50% mortality in our 2:1 group compares favorably with the 51% mortality in their increased I/E ratio group.[7] The difference in the studies lies in the 36% mortality of our 1:2 group and the 89% rate found by Reynolds and Taghizadeh[7] in their lower I/E ratio group. This difference could account for their ability to show a mortality effect of I/E ratio therapy whereas we could not. The discrepancy in mortality results of the two studies may reflect different criteria for beginning mechanical ventilation.

In conclusion, we found that the use of an increased I/E ratio is associated with improved oxygenation for babies receiving mechanical ventilation during the acute phase of HMD. We did not find any relationship of I/E ratio therapy to morbidity or mortality although the suggestion of a greater number of deaths in the 2:1 group deserves a note of caution. Our results also suggest that continuing the use of an increased I/E ratio after the acute phase of HMD does not increase morbidity; however, its use after this period probably offers little benefit since the improvement in oxygenation associated with the increased I/E ratio is most notable during the first several days of life.

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References

1. Reynolds EOR: Effect of alterations in mechanical ventilator settings on pulmonary gas exchange in hyaline membrane disease. *Arch Dis Child* 46:152-159, 1971.

2. Herman S, Reynolds EOR: Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease. *Arch Dis Child* 48:612-617, 1973.

3. Boros SJ, Matalon SV, Ewald R, et al: The effect of independent variations in inspiratory:expiratory ratio and end expiratory pressure during mechanical ventilation in hyaline membrane disease: The significance of mean airway pressure. *J Pediatr* 91:794-798, 1977.

4. Reynolds EOR: Pressure waveform and ventilator settings for mechanical ventilation in severe hyaline membrane disease. *Int Anesthesiol Clin* 12:259-280, 1974.

5. Manginello FP, Grassi AE, Schechner S, et al: Evaluation of methods of assisted ventilation in hyaline membrane disease. *Arch Dis Child* 53:878-881, 1978.

6. Boros SJ: Variations in inspiratory:expiratory ratio and airway pressure wave form during mechanical ventilation: The significance of mean airway pressure. *J Pediatr* 94:114-117, 1979.

7. Reynolds EOR, Taghizadeh A: Improved prognosis on infants mechanically ventilated for hyaline membrane disease. *Arch Dis Child* 49:505-515, 1974.

8. Blake AM, Durbin GM, MacNab AJ, et al: Simplified mechanical ventilation for hyaline membrane disease. *Lancet* 2:1176-1178, 1973.

9. Brown ER, Stark A, Sosenko I, et al: Bronchopulmonary dysplasia: Possible relationship to pulmonary edema. *J Pediatr* 92:982-984, 1978.

10. Gregory GA: Respiratory care of newborn infants. *Pediatr Clin North Am* 19:311-324, 1971.

11. Cotton RB, Stahlman MT, Bender HW, et al: Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. *J Pediatr* 93:647-651, 1978.

12. Northway WH, Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline membrane disease: Bronchopulmonary dysplasia. *N Engl J Med* 276:357-368, 1967.

13. Volpe JJ: Neonatal intracranial hemorrhage: Pathophysiology, neuropathology, and clinical features. *Clin Perinatol* 4:77-102, 1977.

14. Belenky DA, Orr RJ, Woodrum DE, et al: Is continuous transpulmonary pressure better than conventional respiratory management of hyaline membrane disease? A controlled study. *Pediatrics* 58:800-808, 1976.

Macrocytosis and Pure RBC Anemia Caused by Azathioprine

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• Red blood cell macrocytosis is a well-known complication of azathioprine therapy. In a group of 91 patients receiving azathioprine immunosuppressive therapy for renal graft, the mean corpuscular volume determined by an electronic cell counter was substantially higher than in the normal population. Selective erythroid hypoplasia is another known but much less frequent complication of azathioprine use. The case of a child who had a selective erythroid hypoplasia while receiving azathioprine immunosuppressive therapy for renal graft is reported. The patient recovered as the drug therapy was discontinued. With progressive reintroduction of the drug, a second decrease in the hemoglobin was seen when a dose of 2 mg/kg was reached although with a smaller dose, no recurrence of anemia was observed.

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Azathioprine, an immunosuppressive drug with various uses in pediatrics, has a well-known toxic effect on hematopoietic cells. Megaloblastic erythropoiesis, leukopenia, and toxic panmyelopathy have previously been described.[1-4] Selective erythroid hypoplasia is an extremely rare side effect that has recently been described in adult patients.[5,6]

In our population of renal allograft recipients treated with azathioprine, we have noted two consequences of the drug affecting erythropoiesis. The first, RBC macrocytosis, was a common finding. The second, selective erythroid hypoplasia, was found in one case we describe.

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RBC MACROCYTOSIS: PATIENTS AND METHODS

We selected 91 patients with transplants who had normal renal function and no exogenous anemia. Twelve patients were between 6 and 11 years old, 33 were between 12 and 17 years, and 46 were between 18 and 30 years. All patients were receiving azathioprine for a period of at least four months. Red blood cell mean corpuscular volume (MCV) was determined in each patient by an electronic cell counter, each patient having from one to four determinations in a period of three months.

Mean MCVs are given in the Table. Values were compared with normal values published by Dallman,[7,8] which were obtained using the same electronic cell counter model as the one used in this study. In the age groups 12 to 17 years and older than 18 years, the mean MCV was significantly higher than in the normal population ($P < .001$). Of the patients in these two groups, 39 had MCVs greater than 2 SDs from the mean. In the 6-to-11-years-of-age group, the difference was still significant ($P < .02$) although the number of patients was small. Only three patients in this group had MCVs greater than 2 SDs from the mean. Doses of azathioprine ranged between 0.8 mg/kg and 2.9 mg/kg, with a geometric mean of 1.95 mg/kg. Linear regression analysis showed that there was no relation between the RBC MCV and the dose of azathioprine (mg/kg). (MCV = 0.265 × dose + 95.01, $r = -.0192$).

SELECTIVE ERYTHROID HYPOPLASIA: REPORT OF A CASE

A 15-year-old boy had infantile polycystic kidney disease and congenital hepatic fibrosis diagnosed at the age of 6 months. In October 1974, he had end-stage renal disease and required maintenance hemodialysis. Because of portal hypertension, a splenorenal shunt with left nephrectomy and splenectomy were performed in December 1974. Four months later, he successfully received a cadaveric kidney transplant. Daily immunosuppressive therapy consisted of azathioprine, 100 mg (2.5 mg/kg), and prednisone in tapering dosage.

In May 1975, the patient had *Listeria monocytogenes meningitis* that was complicated by seizure activity requiring administration of phenobarbital sodium (2 mg/kg/day). In May 1977, the laboratory tests showed the following values: hemoglobin, 13.5 g/dL; hematocrit, 39.2%; and MCV, 112 fL. One month later, the hemoglobin level had decreased to 9.7 g/dL and two months later, it was 6.5 g/dL.

On Aug 23, 1977, he was admitted to Childrens Hospital of Los Angeles for investigation of anemia. Physical examination showed a short, prepubertal male adolescent with mild features of Cushing's syndrome and severe pallor. His liver was palpable 5 cm below the right costal margin. On admission, the patient was receiving 100 mg of azathioprine daily; 20 mg of prednisone daily; 40 mg (1 mg/kg) of phe-

Values for 91 Patients Receiving Azathioprine*

Age, yr	n	Hemoglobin, g/dL†	MCV, fL†	Normal MCV Mean, fL (−2 SD)‡	P
6-11	12	12.75 ± 1.63	93.14 ± 8.21	86 (76)	<.02
12-17	33	13.05 ± 1.77	93.94 ± 5.25	88 (78)	<.001
≥ 18	46	13.70 ± 1.85	96.58 ± 5.75	90 (80)	<.001

*MCV indicates mean corpuscular volume; fL, femtoliter.
†Mean value ±1 SD.
‡From Dallman.[7]

nobarbital sodium twice daily; and 250 mg of oral penicillin V potassium thrice daily. The hemoglobin level was 6.5 g/dL; hematocrit, 19.5%; MCV, 108 fL; mean corpuscular hemoglobin, 36.6 pg; mean corpuscular hemoglobin concentration, 32.9 g/dL; and reticulocyte count, 0.3%. The WBC count was 4,300/cu mm, with a normal differential cell count and a platelet count of 695,000/cu mm. Inspection of the smear showed anisocytosis and ovalocytosis of the RBCs with many Howell-Jolly bodies; no hypersegmented granulocytes were seen. Iron studies indicated an increased serum iron level of 255 μg/dL, with a transferrin saturation of 96%. Serum folate value was 4.2 ng/mL (normal > 2.3) and serum B_{12} level was 517 pg/dL (normal, 330 to 1,025). Coombs' test was negative. No occult blood was present in the stools.

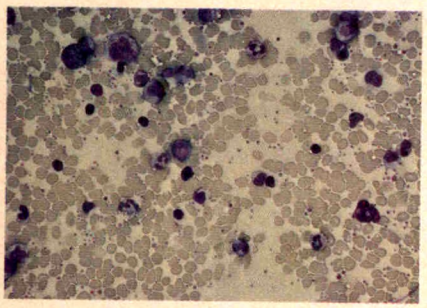


Fig 1.—Patient's bone marrow showing absence of erythroid precursors (Wright's stain, original magnification ×800).

Serum erythropoietin determined by the exhypoxic polycythemic mouse assay showed an activity of 24% uptake of ^{59}Fe. On this assay, normal nonanemic human serum has an erythropoietin activity of 1% or less.[9] Bone marrow examination showed a severe erythroid hypoplasia with a myeloid erythroid ratio of 12:1 (Fig 1). No megaloblastic changes were seen. Megakaryocytes were present in adequate numbers. Serum liver enzyme levels were normal, as were the partial thromboplastin time and the prothrombin time. Total bilirubin value was 0.3 mg/dL. No clinical evidence of graft rejection was detected, and the creatinine level remained in the 0.85 to 1.2 mg/dL range.

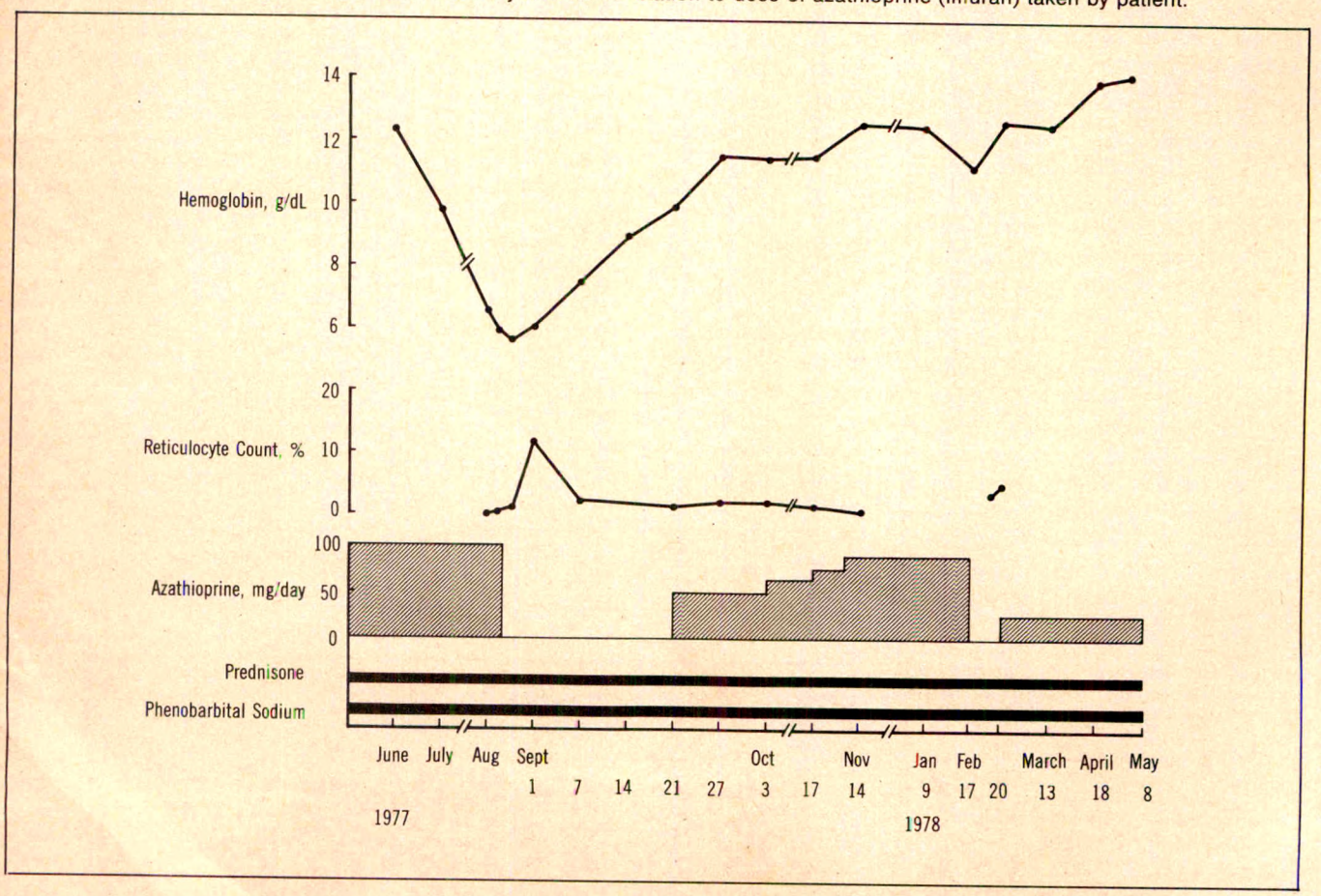
Because azathioprine toxicity was suspected, therapy with that drug was discontinued while treatment with all other medications was continued. No transfusion was given.

Six days after azathioprine therapy was discontinued, the reticulocyte count was 11.1%. Three weeks later, the hemoglobin value was 9 g/dL (Fig 2). Two months later, the hemoglobin value was 11.3 g/dL; hematocrit, 37%; and MCV, 105 fL. The azathioprine was reintroduced at a dose of 1.2 mg/kg/day and progressively increased to 2 mg/kg/day. However, in February 1978, the hemoglobin level began to decrease, and the drug therapy was again discontinued and was then restarted at 0.6 mg/kg/day. Presently, the hemoglobin value is 13.9 g/dL; hematocrit, 42.1%; and MCV, 88 fL. His serum creatinine level is 1.1 mg/dL.

COMMENT

In 1969, Kölle[3] described three types of bone marrow toxic effects induced by azathioprine: megaloblastic changes, defective granulocytopoiesis, and toxic panmyelopathy. In 1975, McGrath et al[5] reported macrocytic changes in 70 renal allograft recipients receiving azathioprine. The severity of the macrocytosis was found to be dose related. In our patients, macrocytosis was also a common finding although no dose relation between MCV and azathioprine was found. In the study of McGrath, the mean geometric dose of azathioprine was 2.83

Fig 2.—Hemoglobin value and reticulocyte count in relation to dose of azathioprine (Imuran) taken by patient.



mg/kg, which is higher than in our group (1.95 mg/kg) and could explain why no dose relation was found in our study. These authors also described two patients who had severe, pure erythroid hypoplasia six and two years after azathioprine therapy was started. In both patients, anemia was corrected by discontinuing therapy with the drug, and as in our patient, azathioprine therapy was reinstituted later at a lower dose, with maintenance of a normal hemoglobin value. More recently, Old et al[6] described two other patients who had a pure RBC anemia develop while receiving azathioprine.

Macrocytosis of RBCs and pure erythroid hypoplasia led us to suspect azathioprine toxicity as the cause of our patient's anemia. The dramatic increase in reticulocyte count and hemoglobin value observed after discontinuation of azathioprine therapy confirmed the suspected diagnosis. Normal serum folate and B_{12} levels excluded deficiency of these vitamins as cause of his anemia. Megaloblastic anemia, but not erythroid hypoplasia, has been described in association with chronic administration of anticonvulsant drugs such as phenobarbital and phenytoin (diphenylhydantoin). In these cases, a low serum folate level was found, and the anemia responded to the oral administration of folate without discontinuation of therapy with the anticonvulsant drugs.[10] Macrocytosis is also seen in chronic liver disease. It is thought to be due to folate deficiency, hemolysis, or acute blood loss,[11] the last two associated with an accelerated maturation and liberation of macrocytic reticulocytes. None of these factors were present in our patient.

Acquired acute pure RBC aplasia is a relatively uncommon disorder in childhood, mainly reported in patients with chronic hemolytic diseases.[12,13] The term "aplastic crisis" is frequently used to describe this transient aplasia associated with a rapid decrease in hemoglobin concentration in patients who already have a decreased RBC survival. There was no evidence of chronic hemolytic disease in our patient. Another cause of acute RBC asplasia is infection.[12-14] Although serologic tests were not performed in our patient to eliminate these possibilities, clinical findings and course did not suggest infection. Autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis; acute renal failure; severe nutritional deficiency; and neoplasm, such as leukemia, lymphoma, and multiple myeloma have also been described with pure RBC aplasia.[15] However, no evidence of any of these diseases have been observed during the period the patient has been followed up. Finally, transient erythroblastopenia of childhood has been described by Wranne,[16] in four children aged 8 months to 4 years. Although this possibility cannot be excluded on clinical grounds, the patient's age and the rapid increase in hemoglobin after discontinuation of azathioprine are more consistent with drug-induced erythroblastopenia.

A high erythropoietin activity has been described[17] in association with renal graft rejection. However, no evidence of rejection was observed in our patient. We interpret the high erythropoietin activity as a normal physiologic response to the anemia. The high serum iron level and transferrin saturation are explained by the selective erythroblastopenia and lack of iron utilization.

Azathioprine, a derivative of mercaptopurine, is a thiopurine. It interferes with de novo purine synthesis, and it inhibits DNA and RNA synthesis. Multiple sites of action have been demonstrated for these thiopurines and their derivatives,[18] including inhibition of purine incorporation into RNA and DNA. Megaloblastosis is thought to be the result of an imbalance between DNA and RNA synthesis, with impairment of the DNA without equivalent impairment of RNA and protein synthesis. According to this hypothesis, azathioprine inhibits DNA synthesis more than RNA synthesis, resulting in megaloblastosis.

The mechanism of selective erythroid hypoplasia is poorly understood. The high erythropoietin activity observed suggests that azathioprine does not inhibit the synthesis of erythropoietin. Since many patients receiving azathioprine have macrocytosis but only a few have selective erythroid hypoplasia, it may be speculated that an additional factor such as infection or a toxin may precipitate the anemia.

Macrocytosis is a common observation in patients taking azathioprine and does not necessitate discontinuation of therapy with the drug. Selective erythroid hypoplasia may seldom be seen and should be suspected in case of rapid development of anemia. Discontinuation of use of the drug is associated with recovery from anemia, and recurrence of anemia is not seen if treatment with the drug is restarted later at a lower dose.

References

1. Bach JB, Dardenne M: The metabolism of azathioprine in renal failure. *Transplantation* 12:253-259, 1971.
2. Dodson WH, Bennett JC: Possible usefulness of azathioprine in severe rheumatoid arthritis. *J Clin Pharmacol* 9:251-258, 1969.
3. Kölle G: Knochenmarksschädigung bei immunsuppressiver therapie der juvenilen rheumatoiden arthritis und des Still-Syndroms mit azathioprine. *Dtsch Med Wochenschr* 94:2268-2273, 1969.
4. Klippel JH, Decker JL: Relative macrocytosis in cyclophosphamide and azathioprine therapy. *JAMA* 229:180-181, 1974.
5. McGrath BP, Ibels LS, Raik E, et al: Erythroid toxicity of azathioprine: Macrocytosis and selective marrow hypoplasis. *Q J Med* 44:57-63, 1975.
6. Old CW, Flannery EP, Grogan TM, et al: Azathioprine-induced pure red cell aplasia. *JAMA* 240:552-554, 1978.
7. Dallman PR: New approaches to screening for iron deficiency. *J Pediatr* 90:678-681, 1977.
8. Koeper MA, Mentzer WC, Brecher G, et al: Developmental change in red blood cell volume: Implication in screening infants and children for iron deficiency and thalassemia trait. *J Pediatr* 89:580-583, 1976.
9. Dukes PP, Hammond D, Shore NA: Comparison of erythropoietin preparations yielding different dose response slopes in the exhypoxic polycythemic mouse assay. *J Lab Clin Med* 74:250-256, 1969.
10. Druskin MS, Wallen MH, Bonagura L: Anticonvulsant-associated megaloblastic anemia. *N Engl J Med* 267:483-485, 1962.
11. Kilbridge TM, Heller P: Determinants of erythrocyte size in chronic liver disease. *Blood* 34:739-746, 1969.
12. Gasser C: Aplasia of erythropoiesis. *Pediatr Clin North Am* 4:445-468, 1957.
13. Chernoff AI, Josephson AM: Acute erythroblastopenia in sickle-cell anemia and infectious mononucleosis. *Am J Dis Child* 82:310-322, 1951.
14. Sears DA, Georges JN, Gold HS: Association of transient pure red cell aplasia with chronic viral hepatitis. *Clin Res* 22:67a, 1974.
15. Krantz SB: Diagnosis and treatment of pure red cell aplasia. *Med Clin North Am* 60:945-958, 1976.
16. Wranne L: Transient erythroblastopenia in infancy and childhood. *Scand J Haematol* 7:76-81, 1970.
17. Ortega JA, Malekzadeh MH, Dukes PP, et al: Exceptionally high serum erythropoietin activity in an anephric patient with severe anemia. *Am J Hematol* 2:299-306, 1977.
18. Beck WS: Megaloblastic anemia unresponsive to vitamin B_{12} or folic acid, in Williams JW (ed): *Hematology*, ed 2. New York, McGraw-Hill Co, 1977, pp 356-362.

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References: 1. Rapp, D. J.: Milk Allergy — From Birth to Old Age. Consultant 14:120, 1974. 2. Cowan, C.C., Brownlee, R.C., DeLoache, W.R., Jackson, H.P., and Matthews, J.P.: A Soy Protein Isolate Formula in the Management of Allergy in Infants and Children. South. Med. J. 62:389, 1969. 3. Clein, N.W.: Cow's Milk Allergy in Infants and Children. Int. Arch. Allergy. 13:245, 1958. 4. Goldman, A.S., Anderson, D.W., Sellars, W.A., Saperstein, S., Kniker, W.T., Halpern, S.R.: Milk Allergy. 1. Oral Challenge with Milk and Isolated Milk Proteins in Allergic Children. Ped. 32:425, 1963. 5. Jung AL, Carr SL: A soy protein formula and a milk-based formula. Clin.Ped. 16:982, 1977. 6. Frier, S. and Kletter, B.: Milk Allergy in Infants and Young Children. Clin. Ped. 9:449, 1970.

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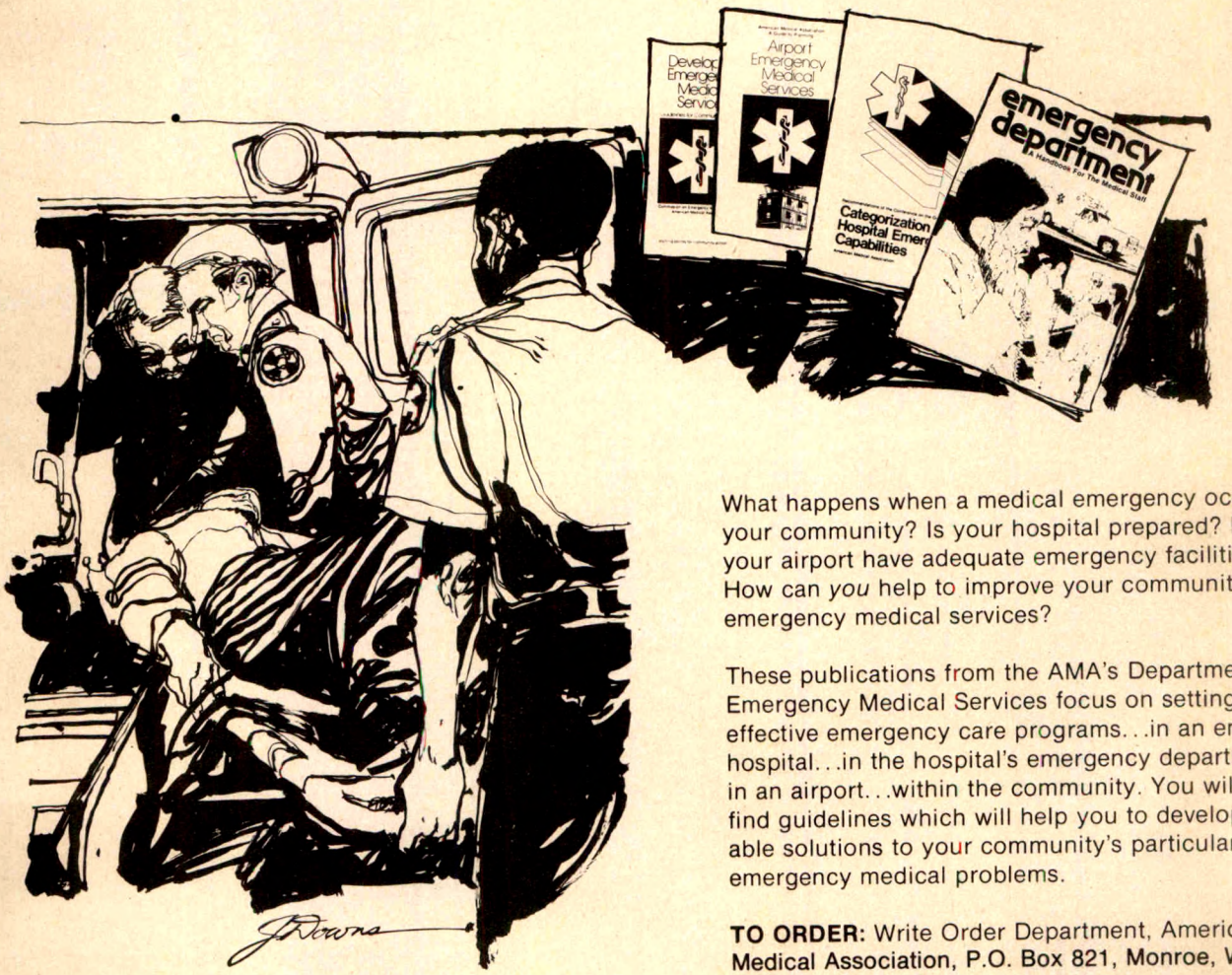

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A 20-year record of proven efficacy

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Reduces hyperactivity, impulsive behavior

Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

Generally well tolerated

Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

*Attention Deficit Disorders: new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

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TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

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References

1. Kugel RB, Scherz RG, Seidel HM, et al. Council on Child Health: Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4):560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al. Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30**:354-359.
3. MacKay MC, Beck L, Taylor R. Methylphenidate for adolescents with minimal brain dysfunction. *NY State J Med* 1973 (Feb.); **73**:550-554.

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Occult Anterior Sacral Meningocele

Thomas E. Sumner, MD; James E. Crowe, MD; Charles R. Phelps II, MD; Roger W. Park, MD

• Anterior sacral meningocele is a rare congenital malformation consisting of a spinal fluid-filled sac in the pelvis communicating by a small neck with the spinal subarachnoid space through a sacral defect. This entity should be considered if the characteristic scimitar sacrum is observed on a pelvic roentgenogram. If signs and symptoms also suggest a meningocele, special studies such as ultrasonography and myelography are indicated to establish the diagnosis of an anterior sacral meningocele. Computerized tomography provides additional evidence of spinal-abdominal extension of this lesion.

(*Am J Dis Child* 134:385-386, 1980)

An anterior sacral meningocele arises from a partial or total defect of the sacrum and coccyx, through which meninges herniate like a cyst. Though rare, it is occult and deaths may occur from meningitis, spontaneous rupture, and obstructed labor. This report describes a young girl with severe constipation and fecal incontinence caused by an anterior sacral meningocele. Sacral roentgenograms invariably disclose some abnormality in this entity.

REPORT OF A CASE

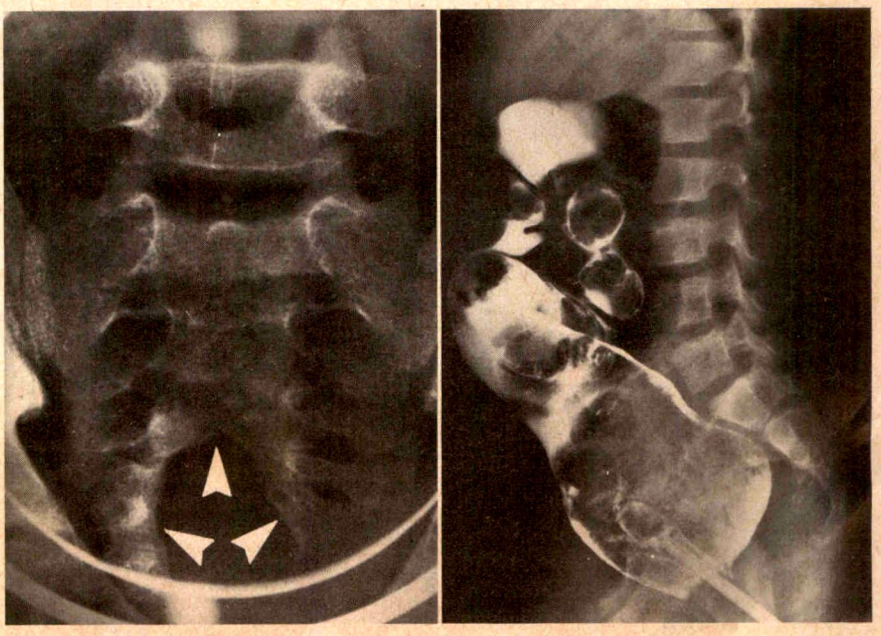
A 7-year-old girl was referred for evaluation of fecal incontinence. As an infant, she continually soiled diapers and subsequent control of bowel function could not be accomplished. Nocturnal enuresis was the only other symptom. Physical examination showed fecal soiling, an extremely large stool-filled rectum, and diminished rectal sphincter tone. Spine roentgenograms demonstrated widening and deformity of the lower aspect of the sacrum (Fig 1, left). The sacral defect was the only congenital defect; maternal history was negative for diabetes. Roentgenogram after barium enema showed anterior displacement of the rectum (Fig 1, right). B mode ultrasound scans demonstrated the sonolucent nature of the mass, indicative of a cystic or fluid-filled lesion (Fig 2, left). Lumbar myelography showed a large presacral meningocele (Fig 2, right). Computerized tomography (CT) demonstrated the presacral fluid-filled mass (Fig 3). Sacral laminectomy showed an anterior sacral meningocele containing lipomatous material. Microscopic examination showed adipose tissue and neural elements within the specimen consistent with a lipomeningomyelocele. Postoperatively, bowel function improved considerably, with cessation of fecal incontinence.

COMMENT

Anterior sacral meningocele is a rare entity, with only about 100 cases reported.[1] Its clinical diagnosis is particularly difficult. Identification of this entity may be elusive unless one is aware of its characteristic roentgenographic features in association with clinical history and physical findings.

The single most important roentgenographic study is the pelvic film, for detection of the characteristic lower sacral widening and deformity. The so-called scimitar or sickle appearance of the sacrum should suggest anterior sacral meningocele. If the sacrum is poorly visualized owing to overlying gas and feces in the colon, we recommend use of a pneumatic compression paddle to improve visualization.[2] Additional confirmatory roentgenographic findings are constrast studies showing displacement or compression of the rectum and myelographic evidence of anterior protrusion of the dural sac into the pelvis. Ultrasound scanning can establish its typical cys-

Fig 1.—Left, Sacral roentgenogram showing typical scimitar sacral defect (arrowheads). Right, Lateral roentgenographic view of barium enema demonstrating anterior displacement of rectum.



From the Departments of Radiology (Drs Sumner, Crowe, and Phelps) and Pediatrics (Drs Sumner, Crowe, and Park), Bowman Gray School of Medicine, Winston-Salem, NC.

Reprint requests to Department of Radiology, Bowman Gray School of Medicine, 300 Hawthorne Rd, Winston-Salem, NC 27103 (Dr Sumner).

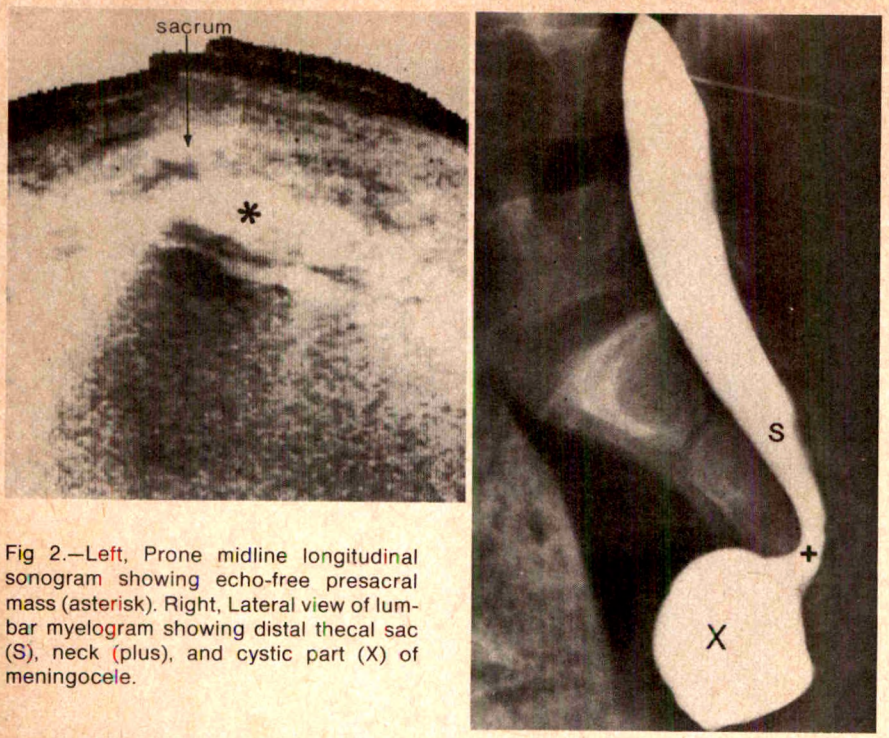


Fig 2.—Left, Prone midline longitudinal sonogram showing echo-free presacral mass (asterisk). Right, Lateral view of lumbar myelogram showing distal thecal sac (S), neck (plus), and cystic part (X) of meningocele.

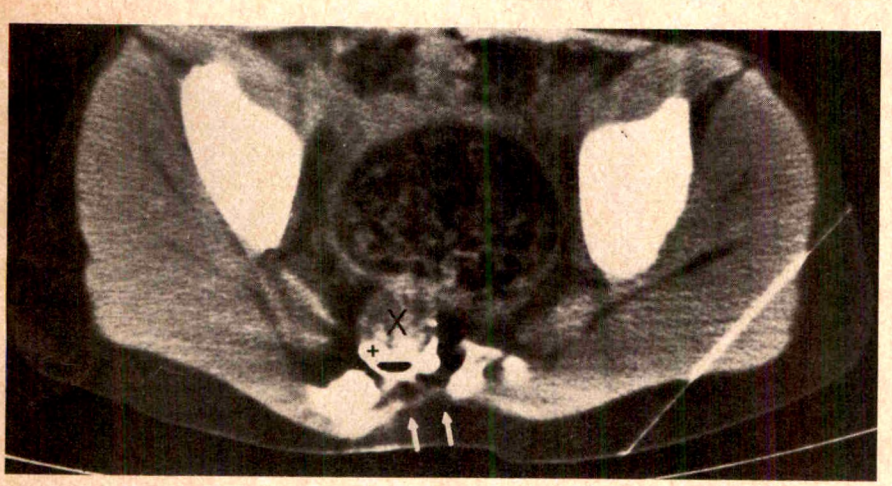


Fig 3.—Computerized tomographic scan at level of sacral defect (arrows) showing presacral mass (X) containing myelographic contrast material (plus).

tic appearance, as illustrated in this case report. If sonography is inconclusive, CT will delineate the suspected presacral mass and confirm its fluid content.

Sacral defects associated with ventral meningocele typically manifest three groups of symptoms: local pressure, local neurological deficits, and central neurological symptoms.[3] Pressure symptoms owing to the meningocele mass include constipation, urinary incontinence or enuresis, and female genital problems such as dysmenorrhea, dyspareunia, and protracted labor. Local neurological symptoms include poor sphincter control, sacral anesthesia, and lower extremity deficits. Common central neurological symptoms include nausea and headache, precipitated by straining or coughing.

In adults, anterior sacral meningocele is more common in females (86%), but the sex ratio among pediatric patients is nearly equal.[4] Age of detection has ranged from the newborn period to the eighth decade. Recent reports indicate a familial tendency;[3,5-7] an X-linked dominant gene may produce this condition.[8] Haddad's[9] review noted a 50% incidence of other congenital anomalies including spinal deformities and duplication defects of the vagina, uterus, and kidneys. Anterior sacral meningocele has been reported in association with Marfan's syndrome.[10] Differential diagnosis includes more common spinal dysraphic anomalies, presacral dermoid cyst, lipoma, chondroma, teratoma, chordoma, neuroblastoma, neurofibroma, as well as inflammatory and metastatic masses.

Surgical treatment is generally advised because spontaneous regression does not occur. The lesion is not innocuous in that deaths have occurred related to rupture of the meningocele, with resultant meningitis.[1] Irreversible nerve root damage may occur when the meningocele is not removed. There are two basic surgical approaches. Sacral laminectomy with ligation, drainage, and/or removal of the meningocele is the preferred procedure in most patients. In selected patients, low transverse abdominal laparotomy with meningocele excision is preferred.[6]

References

1. Amacher AL, Drake CG, McLachlin AD: Anterior sacral meningocele. *Surg Gynecol Obstet* 126:986-994, 1968.

2. Crowe J, Sumner T, Ott D: Improved visualization of the lumbar spine and sacrum in pediatric patients by use of the pneumatic compression paddle. *Radiology* 128:812-814, 1978.

3. Cohn J, Bay-Neilsen E: Hereditary defect of the sacrum and coccyx with anterior sacral meningocele. *Acta Paediatr Scand* 58:268-274, 1969.

4. Vogel EH: Anterior sacral meningocele as a gynecologic problem. *Obstet Gynecol* 36:766-768, 1970.

5. Aaronson I: Anterior sacral meningocele, anal canal duplication cyst and covered anus occurring in one family. *J Pediatr Surg* 5:559-563, 1970.

6. Anderson FM, Burke BL: Anterior sacral meningocele. *JAMA* 237:39-42, 1977.

7. Klenerman L, Merrick MV: Anterior sacral meningocele occurring in a family. *J Bone Joint Surg* 55:331-334, 1973.

8. Say B, Carpenter NJ, Coldwell JG: Anterior sacral meningocele. *JAMA* 237:2602, 1977.

9. Haddad FS: Anterior sacral meningocele: Report of two cases and review of the literature. *Can J Surg* 1:230-242, 1958.

10. Strand RD, Eisenberg HM: Anterior sacral meningocele in association with Marfan's syndrome. *Radiology* 99:653-654, 1971.

Nasal Polymorphic Reticulosis in a Child

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• The case of nasal polymorphic reticulosis in a child is presented. The patient, an 11-year-old adopted boy, complained of nasal stuffiness and pain. Perforation of the nasal septum and ulceration of the hard palate were evident on examination, and an irregular tumor in the nasal cavity was demonstrated by tomography. Biopsy specimen showed atypical lymphoreticular cells within mixed inflammatory infiltrates. He was treated with radiation followed by cyclophosphamide, mercaptopurine, and methotrexate sodium. Despite regression of the palate lesion and a 12-month symptom-free interval, he died of disseminated polymorphic reticulosis 1½ years after diagnosis. We are unable to find a similar reported case in a child.

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Infiltrates of atypical lymphoreticular and mixed inflammatory cells distinguish polymorphic reticulosis from other destructive midfacial lesions.[1-3] Also known as malignant midline reticulosis, it is one of the diseases of diverse causes, which include Wegener's granulomatosis, infections and neoplasms formerly grouped under the term lethal midline granuloma. We wish to point out that polymorphic reticulosis occurs in children as well as adults.

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REPORT OF A CASE

An 11-year-old boy was adopted in the summer of 1977, approximately six months before his first hospital admission. At that time, he complained of nasal pain and, at the time of adoption, had had a nasal septal perforation with heaped up tissue at the edges. A biopsy specimen one month before admission showed chronic inflammation. One week prior to admission, an ulcer of the hard palate was noted after complaints of pain after drinking orange juice. He sniffled often and had an occasional bloody nasal discharge. He had had no fever, weight loss, or decrease in activity, and he continued to play soccer.

His father died at age 33 years of unknown causes. His mother aged 35, a sister aged 8, and a half-sister aged 16 are well.

His height and weight were at the tenth percentile. He had a 2 × 2.5-cm perforation in the cartilaginous and bony nasal septum and a 2 × 1-cm ulcer of the hard palate, with surrounding granulation tissue. Palpable lymph nodes in both anterior cervical chains ranged from 1 to 3 cm in diameter. There was no hepatosplenomegaly or other lymphadenopathy. The rest of the physical examination showed no abnormalities.

His hemoglobin level was 13 g, and his WBC count was 8,000/cu mm, with 63% polymorphonuclear cells, 8% bands, 21% lymphocytes, 5% monocytes, and 3% eosinophils. Platelet count was 520,000/cu mm. The ESR was 45 mm/hr (Wintrobe). Results of urinalysis were normal. The serum albumin level was 4.3 g/dL; and the globulin level was 4.4 g. Immunoglobulin determinations indicated an IgG of 2,422 mg/dL, an IgA of 407 mg/dL, and an IgM of 131 mg/dL. The FTA-ABS and VDRL were negative. Coagulase-positive *Staphylococcus aureus* were cultured from his nose. Results of bone marrow examination were normal.

A lateral roentgenogram of the nasopharynx showed no adenoid mass. Tomograms of the face showed a large, irregular tumor in the nasal cavity (Fig 1).

The palatal and nasal aspects of the lesion were biopsied. In each specimen, the substantia propria contained infiltrates of atypical lymphoreticular cells mixed with smaller numbers of neutrophils, plasma cells, and normal-appearing lymphocytes. Eosinophils were absent. The atypical cells varied in size, most of them having moderate amounts of granular, vacuolated, lightly staining cytoplasm and poorly defined borders. Nuclei were rounded or lobed, with thick membranes. Many nuclei were vesicular, with evenly distributed chromatin and large central nucleoli. Others were folded and densely hyperchromatic, without discernible nucleoli. Mitoses were common. Neither foreign body giant cells nor Reed-Sternberg cells were identified. Infiltrates were particularly dense around vessels, and many small arteries were occluded by thrombi (Fig 2). Focal necrosis, mucosal ulceration, neutrophilic infiltrates, and nuclear debris were prominent in adjacent tissues.

Biopsy specimens of the cervical lymph nodes contained no atypical cellular infiltrates. Nodal capsules were irregularly thickened, and paracortical lymphoid tissue was hypocellular and focally fibrotic. Primary follicles were smaller and fewer than normal. Germinal centers were poorly defined; some contained hyaline-like material, others had collections of epithelioid cells resembling small granulomas. The medullae had normal architecture and cellular composition.

Shortly after the biopsy, the child's care was transferred to a medical center nearer

his home. There, the tumor was debrided, and a week later, x-ray therapy with a cobalt 60 teletherapy machine was begun. During the next 41 days, 4,448 rads were delivered to the tumor, which regressed completely.

One month later, the boy began receiving chemotherapy consisting of induction with vinblastine sulfate (Velban), prednisone, cyclophosphamide (Cytoxan), and methotrexate sodium, and maintenance with mercaptopurine, cyclophosphamide, and methotrexate. His course during chemotherapy was relatively uneventful. He appeared chronically ill, but his weight remained stable. The site of the palatal lesion remained healed, and there was no evidence of systemic disease. Lesions of herpetic stomatitis periodically appeared and resolved. Treatment was discontinued in November 1978, 11 months after it was begun, because of neutropenia and thrombocytopenia.

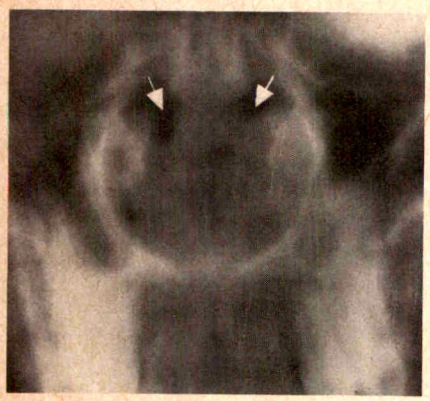
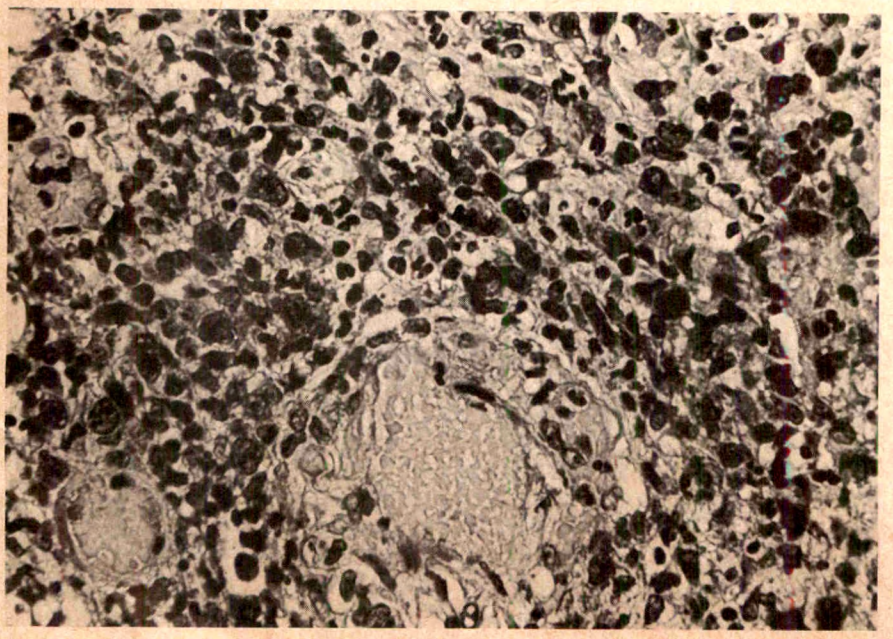


Fig 1.—Tomogram shows nasal cavity is expanded by irregular tumor (arrows). Apparent defect at bottom of bony rim is normal depression of nasopalatine recess.

The boy was hospitalized three times in December 1978 because of recurrent hepatitis. In each instance, admission was prompted by the development of high fever, anorexia, and hepatomegaly, and on each occasion, liver function subsequently improved without specific treatment. During the first of these admissions, tests to detect viral infection were negative except for a titer of 1:640 to the Epstein-Barr virus. A screening test for heterophile antibodies was negative. A convalescent titer for Epstein-Barr virus was again 1:640.

He was hospitalized for the last time in March 1979, again with symptoms of hepatitis and cachexia. He was jaundiced and his liver edge extended 5 cm below the right costal margin. A submental lymph node had enlarged to nearly 5 cm in diameter, and smaller nodes were palpable in cervical, supraclavicular, and axillary areas. The SGOT value was 2,055 IU/L, the alkaline phosphatase level was 1,580 IU/L, and the bilirubin level was 2.4 mg/dL (0.7 mg/dL direct). His liver function improved briefly during hospitalization, but it quickly deteriorated again. After the possibility of extrahepatic biliary obstruction was excluded by ultrasonography and liver scan, the liver and submental lymph node were biopsied. Liver failure and the boy's poor general condition precluded further chemotherapy. He was discharged a month after admission and died three days later at home. An autopsy was performed.

Fig 2.—Palatal lesion showing anaplastic lymphoreticular cells and mixed inflammatory cells, including neutrophils and nuclear debris in tissue adjacent to small vessels. Vessels in lower center and lower left of micrograph are occluded by fresh thrombi; wall of larger vessel is edematous and contains a few infiltrating inflammatory cells (hematoxylin-eosin, original magnification ×680).



RESULTS

The biopsied submental lymph nodes and nearly all lymphoid tissue examined at autopsy were involved by polymorphic reticulosis. The normal follicular architecture was replaced by extensive coagulation necrosis and nodules of atypical infiltrates closely resembling those in the nasopalatal lesion. The reticulin pattern was preserved throughout the areas of necrosis. The few nodes without necrosis or abnormal infiltrates were fibrotic and generally depleted of lymphoid cells. The trabecular and vascular structures of the spleen were preserved, but the tissue was otherwise hypocellular, consisting of broad areas of fibrosis and necrosis. Sparse infiltrates of polymorphic reticulosis were evident near splenic arterioles within the remnants of lymphoid follicles. The thymus was atrophic, but it contained no atypical infiltrates.

Liver tissue obtained at autopsy, like that of the biopsy specimen, contained scattered foci of parenchymal necrosis. Many of these zones were microscopic; others were large enough to span two or more lobules without a consistent pattern of distribution. Polymorphic reticulosis cells were present within the necrotic tissue and were scattered through the liver sinusoids. Kupffer cell hyperplasia and erythrophagocytosis were particularly evident near the areas of necrosis.

Polymorphic reticulosis infiltrates and accompanying necrosis formed nodular aggregates in the subcapsular tissues of the kidneys. Atypical cells were present in tissues adjacent to shallow mucosal ulcerations in the terminal ileum.

COMMENT

The clinical features of polymorphic reticulosis are the same as those of lethal midline granuloma, first described in detail by Stewart[4] in 1933.

The course may last for several years, generally beginning with nasal stuffiness, nasal obstruction, or rhinorrhea. There may be crusting of the nasal mucosa and sinusitis. Mucosal ulceration ensues, and necrosis extends to involve adjacent bone and cartilage. The nasal discharge becomes thicker and malodorous, and there is usually pain and tenderness in the affected area. The patient often experiences fevers, malaise, and weight loss. If untreated, the lesion advances, destroying nasal and paranasal structures that may include the orbit, mouth, base of the skull, area cribrosa, and brain until death from inanition, infection, or hemorrhage results. The disease typically occurs in men in the fifth or sixth decade of life. Askin[5] stated that the lesion affects children, but to our knowledge, no cases have been reported.

Kassel et al[2] reviewed the literature of lethal midline granuloma and concluded that, except for specific infections and solid tumors, all of such cases would be in three categories: Wegener's granulomatosis, lymphoma, and polymorphic reticulosis (malignant midline reticulosis).

Histologically, polymorphic reticulosis consists of infiltrates of atypical lymphoreticular cells and mixed inflammatory cells and stellate areas of tissue necrosis. The infiltrates advance into adjacent soft tissue, bone, and cartilage, followed by necrosis and collapse. The underlying reticulin pattern is often preserved in the necrotic zones. Vessels are involved secondarily; adventitial and intimal infiltrates, endothelial proliferation, and thrombosis are often prominent. Similar vascular involvement has been described in conventional lymphomas involving the nose.[1]

The atypical cells have round or elongated nuclei with irregular or folded contours. Chromatin is usually scanty although densely hyperchromatic forms are also seen. Nucleoli may be prominent. Cytoplasmic volume is variable; cellular outlines are usually indistinct and some cells may contain phagocytized debris. These cells may form small monocellular nests, and their appearances have led in the past to diagnoses of atypical reticulum cell sarcoma and histiocytic or mixed lymphocytic-histiocytic lymphoma. Atypical cells are usually admixed, however, with lymphocytes, plasma cells, histiocytes, and polymorphonuclear leukocytes, sometimes including small numbers of eosinophils. Multinucleated cells are usually absent. This inflammatory character of the infiltrate, its loose, noncohesive growth, and the extensive necrosis help distinguish polymorphic reticulosis from most conventional lymphomas. Cells resembling Reed-Sternberg cells are not found in polymorphic reticulosis.

Wegener's granulomatosis is characterized by a combination of necrotizing arteritis, granulomatous inflammation, abundant inflammatory infiltrates including eosinophils, and the absence of cellular atypia. Most patients will also have clinical evidence of pulmonary and renal involvement. Both Wegener's granulomatosis and primary lymphomas of the nose occur in children.[6,7]

Embryonal rhabdomyosarcoma and nasopharyngeal carcinoma also cause destructive nasal lesions in children. Lack of differentiating features may leave the identity of either tumor in doubt and may prompt consideration of lymphomas or other tumors in some instances. Neither should be confused with the loose, pleocellular infiltrates of polymorphic reticulosis.

Opinions vary regarding the nature of polymorphic reticulosis and its relationship to other destructive midfacial lesions.[1,2,8-10] Despite this, authors agree that the appropriate treatment differs with each entity and that a specific diagnosis should be made even if repeated biopsies are necessary.[8,11-13]

The facial lesion of polymorphic reticulosis usually resolves after adequate radiotherapy.[11,12] Some patients, like our own, however, eventually die of a disseminated disease despite initial response to x-ray treatment.[11,14]

Joel E. Hass, MD, associate pathologist, and Ronald L. Chard, Jr, MD, Associate Director of the Division of Hematology/Oncology at the Children's Orthopedic Hospital and Medical Center, Seattle, provided important histological material and information regarding this patient's treatment and clinical course.

References

1. Eichel BS, Harrison EG Jr, Devine KD, et al: Primary lymphoma of the nose including a relationship to lethal midline granuloma. *J Surg* 112:597-605, 1966.

2. Kassel SH, Echevarria RA, Guezzo FP: Midline malignant reticulosis. *Cancer* 23:920-935, 1969.

3. McGuirt WF, Rose EF: Lethal midline granuloma: A pathological spectrum. *J Laryngol Otol* 90:459-466, 1976.

4. Stewart JP: Progressive lethal granulomatous ulceration of the nose. *J Laryngol Otol* 48:657-701, 1933.

5. Askin FB: Nose, nasopharynx, larynx and trachea, in Kissane JM (ed): *Pathology of Infancy and Childhood*, ed 2. St Louis, CV Mosby Co, 1975, p 451.

6. Jaffe BF: Pediatric head and neck tumors: A study of 178 cases. *Laryngoscope* 83:1644-1651, 1973.

7. Roback SA, Herdman RC, Hoyer J, et al: Wegener's granulomatosis in a child. *Am J Dis Child* 118:608-614, 1969.

8. Michaels L, Gregory MM: Pathology of 'non-healing (midline) granuloma.' *J Clin Pathol* 30:317-327, 1977.

9. Friedman I, Sando I, Bakany TH: Idiopathic pleomorphic midfacial granuloma (Stewarts type). *J Laryngol Otol* 92:601-611, 1978.

10. Douglas AC, Anderson TJ, MacDonald M: Midline and Wegener's granulomatosis. *Ann NY Acad Sci* 278:618-635, 1976.

11. Fechner RE, Lamppin DW: Midline malignant reticulosis: A clinicopathologic entity. *Arch Otolaryngol* 95:467-476, 1972.

12. McDonald TJ, DeRemee RA, Harrison EG Jr, et al: The protean clinical features of polymorphic reticulosis (lethal midline granuloma). *Laryngoscope* 86:936-945, 1976.

13. McGuirt FW, Rose EF: Lethal midline granuloma: A pathological spectrum. *J Laryngol Otol* 90:459-466, 1976.

14. Yesus YW: Midline malignant reticulosis: Case report. *Mo Med* 74:375-378, 1977.

Friedreich's Ataxia With Acute Cardiomyopathy

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• Friedreich's ataxia (FA) is a progressive, spinocerebellar degenerative disease. Onset is generally in the second decade of life, occurring as a neurologic degenerative process. Most, if not all, patients have an associated cardiomyopathy, which is frequently the cause of death. We studied two siblings who had FA with acute cardiomyopathy at 3 and 5 years of age, respectively, and in whom the classic nervous system signs developed, only later. The diagnosis of FA should be considered in patients of any age who have unexplained cardiomyopathy.

(*Am J Dis Child* 134:390-393, 1980)

Friedreich's ataxia (FA) is an autosomal recessive form of spinocerebellar degeneration, characterized by relentless and progressive ataxia, muscle weakness, dysarthria, sensory abnormalities, areflexia, and skeletal deformities. The onset is usually early in the second decade of life, and in most patients a slowly progressive cardiomyopathy develops. Although the cardiomyopathy is variable in its clinical occurrence and may remain asymptomatic throughout the course of the disease, cardiopulmonary sequelae are the usual cause of death in this disease. We studied two siblings with FA that had an unusual clinical course. Both, when younger than 5 years of age, initially had an acute cardiomyopathy; only later did neuromuscular disease develop. Death occurred in both children before they were 12 years old, and, at the time of postmortem studies, typical CNS and cardiac findings of FA were confirmed. The importance of considering the diagnosis of FA in any patient in whom an unexplained cardiomyopathy develops must be emphasized.

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REPORT OF CASES

Case 1.—A 6-year-old girl was transferred to Good Samaritan Hospital, Phoenix, Ariz, because of refractory congestive heart failure (CHF). She had been healthy until 3 years of age, when CHF developed, and her condition was evaluated at the University of Minnesota. Diagnostic studies performed at that time included an ECG, chest roentgenograms, and a cardiac catheterization. A diagnosis of an acute cardiomyopathy was made. Her 6-year-old brother had had a similar episode of CHF one year earlier and was noted subsequently to have truncal and upper extremity ataxia. Despite the normal results on neurologic examination, both children were considered to have FA. Over the following three years, the patient had recurrent bouts of CHF that required frequent hospitalizations. Throughout this period, she continued to walk well, and her parents did not notice any neuromuscular problems. Her developmental progress was normal. There was no history of consanguinity or family history of neuromuscular or cardiac disease.

Physical examination on admission to the hospital showed a chronically ill and cachectic child. Vital signs included the following values: pulse, 124 beats per minute; blood pressure, 85/40 mm Hg; respirations, 48/min; and temperature, 37 °C. The patient had mild intercostal retractions, nasal flaring, and basilar rales bilaterally. A sinus tachycardia with a gallop rhythm was noted. The liver was palpable 5

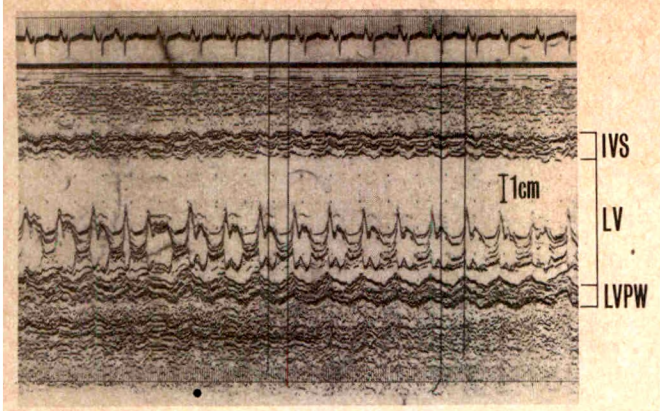

Fig 1.—Echocardiogram showing nonobstructive cardiomyopathy with evidence of left ventricular enlargement (LV) and mild hypertrophic changes of left ventricular posterior wall (LVPW) and intraventricular septum (IVS) in patient 2.

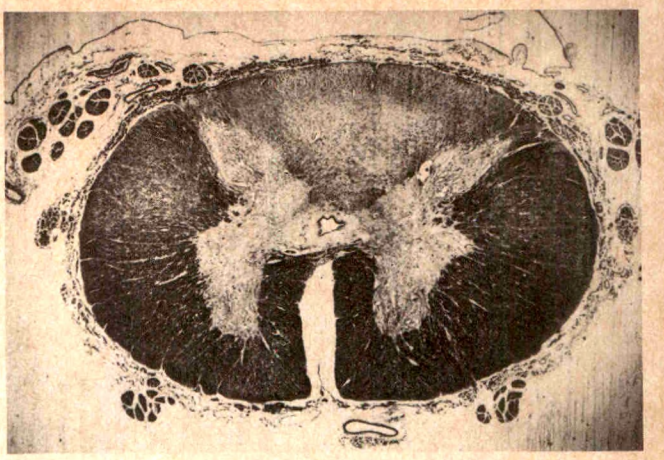

Fig 2.—Transverse section of the spinal cord showing demyelination of the posterior columns, lateral corticospinal and posterior spinocerebellar tracts, and dorsal nerve roots (luxol-fast blue, original magnification ×2.5).

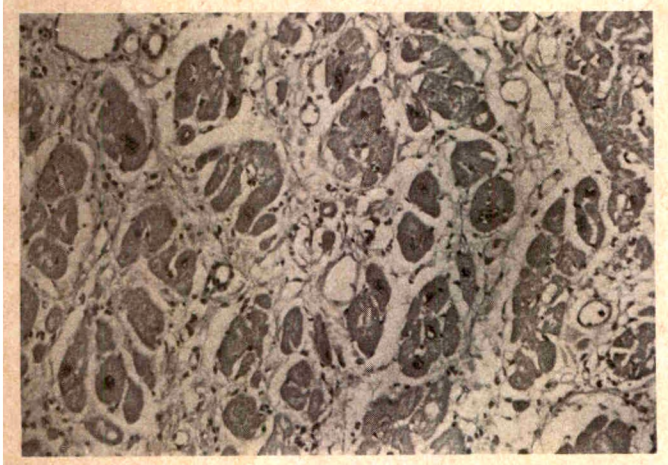

Fig 3.—Section of myocardium showing areas of focal degeneration and atrophy of muscle fibers with enlarged hyperchromatic nuclei (hematoxylin-eosin, original magnification ×40).

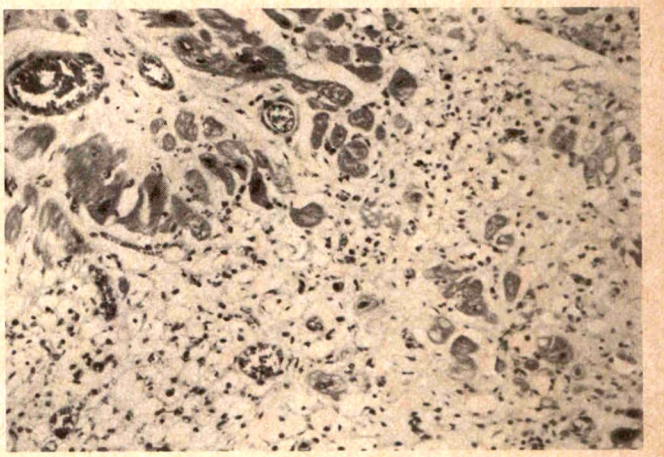

Fig 4.—Section myocardium demonstrating severe interstitial fibrosis and scattered inflammatory cells (hematoxylin-eosin, original magnification ×40).

cm below the right costal margin, and there was moderate peripheral, facial, and anterior chest wall edema. A pes cavus deformity was noted and kyphoscoliosis was present. The child was weak and had evidence of generalized muscular atrophy. Dysmetria was present, and vibratory sense was diminished. The cranial nerves were normal. The deep tendon reflexes were absent.

Results of laboratory investigations showed that complete blood cell count (CBC), results of urinalysis, and serum electrolyte levels were normal. An ECG showed sinus tachycardia, combined atrial hypertrophy, left ventricular hypertrophy, and inverted T waves. Chest roentgenograms demonstrated an enlarged heart with evidence of pulmonary edema. There were no pulmonary infiltrates.

The hospital course was characterized by progressive weakness, increasing tachypnea and persistent tachycardia, and neurologic deterioration despite medical management. The patient had a cardiac arrest and died on the second hospital day.

Case 2.—A 12-year-old boy (sibling of case 1) was admitted to Good Samaritan Hospital because of congestive heart failure. At 5 years of age, congestive failure developed, that required hospitalization and treatment with digitalis and diuretics. The cardiac symptoms resolved over several weeks and required no further medical management. At 6 years of age, his condition was evaluated at the University of Minnesota because of his sister's myocardiopathy. He was noted to have an ataxic gait, mild upper extremity intention tremor, and loss of deep tendon reflexes. There was no apparent heart disease at that time, and the child was fully active. At 10 years of age, he was noted to have scoliosis and bilateral pes cavus deformities. At age 12 years, he had a recurrence of CHF. Six months prior to his final hospital admission, progressive shortness of breath, chest pain, orthopnea, and peripheral edema developed. The ataxia worsened steadily over this six-month period, and signs of dysarthria and nystagmus developed.

Physical examination on admission to the hospital showed a thin, chronically ill, and depressed 12-year-old boy in moderate respiratory distress. His height was 155 cm; his weight, 36.4 kg. Vital signs included the following values: pulse, 100 beats per minute; blood pressure, 100/60 mm Hg; respirations, 34/min; and temperature,

Fig 5.—Photograph showing thrombosis of superior vena cava (arrow) and innominate veins.

37 °C. The examination of head and neck gave normal results except for a diffuse 3 × 3-cm, tender, nonerythematous, right supraclavicular mass. There were moderate intercostal retractions, nasal flaring, and bilateral basilar rales. A grade 2/6 systolic murmur was heard, and there was a persistent gallop rhythm. The neck veins were distended, and the liver was palpable 5 cm below the right costal margin. Peripheral pulses were weak. There were severe pes cavus deformities and moderate thoracic kyphoscoliosis. Results of examination of the cranial nerves were normal except for horizontal nystagmus. There was no optic atrophy. Vibratory and position senses were lost bilaterally, but pain and touch were intact. Generalized muscle weakness and atrophy were present. Truncal ataxia, dysmetria, and intention tremor were severe. The deep tendon reflexes were absent, and Babinski's signs were present bilaterally.

Laboratory investigations yielded a normal CBC and serum electrolyte and chemistry levels. A fasting blood glucose level was 88 mg/dL. Chest roentgenograms showed a large heart and scoliosis. Subsequent films showed persistent cardiomegaly, left pleural effusion, and bilateral nodular infiltrates. An ECG showed right axis deviation with left ventricular and right atrial hypertrophy, occasional premature ventricular contractions, and intermittent atrial fibrillation. Echocardiography showed poor myocardial contractility, severe left ventricular dilation, and prolonged systolic time intervals (Fig 1). There was no evidence of hypertrophic subaortic stenosis. Severe dilation of the left atrium was also noted. Sonography and computerized tomography of the neck demonstrated the presence of a solid mass.

The clinical course was characterized by progressive cardiac decompensation. Conventional therapy was unsuccessful, and the patient died after one month.

The autopsy findings in both siblings were virtually identical and were characteristic of FA. In the spinal cord, the posterior columns were shrunken and degenerated, as were the dorsal nerve roots. Atrophy of Clarke's columns and the posterior spinocerebellar tracts was virtually complete in the thoracic cord. The pyramidal tracts showed progressive fiber loss as they descended, and degeneration of the fasciculus gracilus and cuneatus was noted. The degenerated tracts were gliotic, with myelin loss visible macroscopically (Fig 2). Sections of the pons and the medulla showed diffuse loss of cells in the pyramidal tracts, and there was mild dropout of Purkinje's cells within the cerebellum. The cerebral hemispheres were normal.

The lesions in the heart were also identical, demonstrating a prominent cardiomyopathy with severe replacement of the myocardium with collagen and secondary mural thrombi. Areas of focal degeneration of muscle fibers with enlarged hyperchromatic and frequently bizarre nuclei were characteristic (Fig 3). There was no evidence of coronary vascular abnormalities, and no abnormal calcifications were noted. Interstitial fibrosis in many areas was severe, and scattered round cell infiltrates were seen as a response to active degeneration of myocardial fibers (Fig 4). There was extensive thrombosis in the pulmonary venous system and superior vena cava and its tributaries (Fig 5), the latter resulting in a large neck mass.

COMMENT

Friedreich's ataxia was first described in 1861[1] and is the most common of the hereditary ataxias. Neuropathologic studies performed in the early 1900s defined this disease more clearly, but there has been little progress made toward understanding the cause and pathogenesis of FA, despite more recent clinical, biochemical, and neuropathologic investigations. In many patients, glucose intolerance and diabetes mellitus develop.[2-4] Several investigators have demonstrated mild hyperbilirubinemia, slow pyruvate oxidation, elevated serum and urine alanine levels, low CSF taurine and aspartic acid levels, elevated levels of urine taurine, and elevated levels of urine β-alanine and β-aminoisobutyric acid,[4,5] but these changes are not seen in all patients with FA.

Clinical criteria for the diagnosis of FA have been established[6] and include the following: (1) autosomal recessive inheritance, (2) onset before the end of puberty, (3) progressive and relentless ataxia without remission and usually accompanied by muscle weakness, (4) dysarthria, (5) absent or severe decrease in vibratory and/or position sense, (6) absence of deep tendon reflexes in the lower limbs, (7) progressive development of pes cavus and kyphoscoliosis, and (8) progressive cardiomyopathy. Electromyography and motor nerve conduction rates are normal, but sensory nerve conductions (evoked potentials) are diminished or absent. Intellectual impairment, nystagmus, deafness, vestibular signs, optic atrophy, and autonomic dysfunction are variably present.

Cardiac involvement in FA has been well documented and was recognized pathologically in three of the initial six cases described by Friedreich.[1] Most patients ultimately show evidence of cardiac involvement on clinical studies, roentgenograms, or ECGs.[2-4,7-10] Echocardiography is a useful technique in evaluating the severity of cardiac involvement and provides a sensitive means for the diagnosis of hypertrophic cardiomyopathy.[11] Hewer,[8] in a review of 27 fatal cases of FA, found that over 50% died of cardiac complications and that 75% had evidence of cardiac involvement during life. The cardiomyopathy is often present and asymptomatic at the onset of the illness and may not cause symptoms until late in the course of the disease. It does not seem to correlate with the severity of the neurologic signs. Severe cardiomyopathy early in the course or prior to the onset of neurologic signs occurs, but is distinctly unusual.[12] Brusca et al[13] in 1965 also stressed that cardiac involvement may be the sole expression of the disease in some instances. The cardiomyopathy is degenerative in type and seems unrelated to electrolyte disorders, hypoglycemia, endocrine dysfunction, infectious agents, or coronary vascular disease. Widespread small coronary vessel involvement has been inconsistently noted at necropsy,[14] and medial thickening of cardiac arterioles associated with arteritis and endothelial proliferation has been described. This, however,

does not seem to be a primary etiologic factor in the development of the cardiomyopathy.[9]

Electrocardiographic changes occur in most patients with FA,[2-4,7,8] and Thoren[10] in 1964, studying 49 patients, showed a 92% incidence of abnormal tracings. Electrocardiographic abnormalities documented in these studies include atrial fibrillation, varying degrees of heart block, ventricular tachycardia, T-wave flattening or inversions, nonspecific ST-T-wave changes, and atrial and ventricular hypertrophy.

Sanchez-Casis et al[7] in 1976 reviewed the cardiac pathology seen in FA. The most constant finding was macroscopic cardiomegaly with some degree of ventricular hypertrophy. Atherosclerotic plaques involving major branches of the coronary arteries were also noted but were not considered to be of hemodynamic significance. Histologic changes included diffuse myocardial fibrosis, most preponderant in the anterior wall of the left ventricle and septum, and focal degeneration of cardiac muscle fibers. One additional finding not previously described was the presence of granular deposits of calcium and iron within muscle cells. In view of these abnormalities, the authors concluded that "a cardiomyopathy, hypertrophic in type and occasionally obstructive, appears to be an integral part of Friedreich's ataxia."

More recent reports have suggested an association between the cardiomyopathy of FA and idiopathic hypertrophic subaortic stenosis (IHSS).[11,15,16] Smith et al,[11] reviewing 11 patients with FA, found one third to have evidence of hypertrophic cardiomyopathy (HCM) by echocardiography, with two of these patients showing clinical features of left ventricular obstruction typical of IHSS. The authors, therefore, suggested that "HCM is the specific cardiomyopathy of classical FA and that both the neurologic and myocardial defects represent pleiotropic effects of the same deleterious gene."

The treatment of FA is unsatisfactory, and no specific therapy is available. In view of the substantial number of cases with associated cardiomyopathy, early recognition and treatment of this complication may favorably influence the prognosis. Congestive heart failure secondary to the cardiomyopathy is generally treated with digitalis and diuretics, although in the occasional patient with obstruction to the left ventricular outflow, digitalis may not be beneficial. The abnormalities seen on ECGs (ST-T–wave changes) from patients with FA seem to be consistent with increased calcium flux into the cardiac muscle cells. Therefore, agents that decrease this mechanism will reduce heart rate, decrease myocardial oxygen demand, and increase cardiac efficiency. Increased taurine intake and administration of verapamil reduce calcium influx and may be useful in modifying the cardiomyopathy or preventing its progression.[9] These latter drug approaches, however, need further investigation.

Our patients had an unusual presentation of FA in which acute cardiomyopathy with congestive heart failure occurred in early childhood without initial neurologic abnormalities. The classic neurologic symptoms and signs of FA developed only later. The children died, with evidence of severe chronic cardiomyopathy, at 6 and 12 years of age, respectively. There was no evidence of hypertrophic subaortic stenosis. In addition, these patients had unusual edema of the anterior chest wall and neck, which at postmortem examination was found to be secondary to venous thrombosis of the superior vena cava and its tributaries. This was presumably secondary to poor myocardial contractility and venous stasis. In view of our patients' presentation, we stress the need to consider the diagnosis of FA in patients of all ages who have acute cardiomyopathy of unknown cause. Careful history and neurologic and skeletal examinations in children with unexplained heart failure may lead to an early diagnosis of FA.

Barbara Bengtson assisted in the preparation of this manuscript.

Nonproprietary Name and Trademark of Drug

Verapamil–*Isoptin*.

References

1. Friedreich N: Über degenerative Atrophie der spinalen Hinterstränge. Read before the Kongressitzungskericht der Deutschen Aerzte und Naturforscher, Speier, 1861.
2. Tyrer JH: Friedreich's ataxia, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology*. New York, Elsevier-North Holland Publishing Co, 1975, vol 22, pp 319-364.
3. Andermann E, Remillard GM, Goyer C, et al: Genetic and family studies in Friedreich's ataxia. *Can J Neurol Sci* 3:287-301, 1976.
4. Barbeau A: Friedreich's ataxia 1976: An overview. *Can J Neurol Sci* 3:389-397, 1976.
5. Barbeau A: Friedreich's ataxia 1978: An overview. *Can J Neurol Sci* 5:161-165, 1978.
6. Barbeau A: Friedreich's ataxia: Cooperative study, phase two: Statement of the problems. *Can J Neurol Sci* 5:57-59, 1978.
7. Sanchez-Casis G, Cote M, Barbeau A: Pathology of the heart in Friedreich's ataxia: Review of the literature and report of one case. *Can J Neurol Sci* 3:349-354, 1976.
8. Hewer RL: The heart in Friedreich's ataxia. *Br Heart J* 31:5-14, 1969.
9. Huxtable RJ: Cardiac pharmacology and cardiomyopathy in Friedreich's ataxia. *Can J Neurol Sci* 5:83-91, 1978.
10. Thoren C: Cardiomyopathy in Friedreich's ataxia: With studies of cardiovascular and respiratory function. *Acta Paediatr Scand* 53(suppl 153):1-131, 1964.
11. Smith ER, Sangalang VE, Heffernan LP, et al: Hypertrophic cardiomyopathy: The heart disease in Friedreich's ataxia. *Am Heart J* 94:428-434, 1977.
12. Thilenius OG, Grossman BJ: Friedreich's ataxia with heart disease in children. *Pediatrics* 27:246-254, 1961.
13. Brusca AG, Politi G, Lavezzaro G, et al: Les alterations electrocardiographiques de la maladie de Friedreich: A propos de 9 cas. *Presse Méd* 73:963-964, 1965.
14. James TN, Fisch C: Observations on the cardiovascular involvement in Friedreich's ataxia. *Am Heart J* 66:164-175, 1963.
15. Ruschhaupt DG, Thilenius OG, Cassels DE: Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis. *Am Heart J* 84:95-102, 1972.
16. Boehm TM, Dickerson RB, Glasser SP: Hypertrophic subaortic stenosis occurring in a patient with Friedreich's ataxia. *Am J Med Sci* 260:279-284, 1970.

Bilateral Carpal Tunnel Syndrome in an Adolescent

Mark H. Feingold, MD; Ernest Hidvegi, MD; Samuel J. Horwitz, MD

• A 13-year-old boy with nocturnal paresthesias of the hands was shown to have bilateral carpal tunnel syndrome by electrodiagnosis. Surgical findings included thickening of the transverse carpal ligament and local anomalies of tendon and muscle. Surgical correction produced prompt relief.

(*Am J Dis Child* 134:394-396, 1980)

Carpal tunnel syndrome (CTS) is a peripheral entrapment neuropathy of the median nerve caused by localized pressure on that structure as it courses beneath the flexor carpal retinaculum. A common disorder of adults, it is distinctly unusual during childhood. We studied a case of bilateral CTS with onset in adolescence.

REPORT OF A CASE

The patient, a 13-year-old boy, had been in good health until eight months earlier, when he began to be awakened by late nocturnal pain and numbness. He also complained of "pins and needles" and "burning" in both hands, specifically affecting the thumbs, index and middle fingers, and lateral side of the ring fingers. He obtained some relief by shaking or wringing his hands and could then return to sleep. He complained of no weakness, pain, or loss of feeling during the daytime hours. Three months before his symptoms began, he had started weight lifting and riding a minibike, but had operated no other power equipment. His symptoms were aggravated after certain daytime activities, such as shoveling snow or writing a great deal. Only his mother was available to provide a family history, and she was unaware of similar symptoms in any relatives. The patient's statural growth had been normal, and puberty had begun at 11 years of age. His history was noncontributory, except for a probable viral illness one year prior to onset of his hand symptoms. This illness had been manifested by generalized weakness and myalgia, abdominal pain, fever, scleral injection, and transient proteinuria. Extensive evaluation at that time failed to show a specific cause, and his symptoms were fully resolved after one month. An asymptomatic, nonossifying fibroma of the proximal metaphysis of the right femur was discovered incidentally, when the patient bruised his knee. There had been no other skeletal complaints or findings.

Physical examination showed a robust, muscular boy with a height of 161 cm (75th percentile) and a weight of 68 kg (97th percentile). Blood pressure was 134/55 mm Hg supine. Physiognomy was normal, and puberty was estimated at Tanner's stage 3-4. Many freckles were present, but there were no neurocutaneous lesions. The joints all had full range of motion. The arms and hands were symmetric, and there was no atrophy of the thenar eminences. Finger strength was normal, and he was able to perform full-length pushups with weight supported on the outstretched fingertips. Sensory examination, including light touch, pinprick, position and vibratory senses, graphesthesia, two-point discrimination, and stereognosis, was entirely normal. Tinel's sign (pain on tapping of the median nerve along its course at the wrist) and Phalen's sign (hand pain and paresthesia after acute volar flexion at the wrist) were absent. The radial pulses were equal and normal. The results of the remainder of the neurological examination were normal, including tests of affect, intelligence, cranial nerves, motor strength, cerebellar function, and deep tendon and superficial reflexes.

Roentgenograms of both wrists were normal. Other studies with normal results included complete blood cell count, urinalysis, and BUN, random glucose, serum thyroxine, uric acid, cholesterol, protein electrophoresis, immunoelectrophoresis, folic acid, and vitamin B_{12} levels.

Needle electromyography (EMG) was carried out in the left pronator teres, flexor carpi radialis, flexor carpi ulnaris, first dorsal interosseous, and in the abductor pollicis brevis muscles bilaterally. Only the abductor pollicis brevis showed an abnormality, which consisted of increased insertion activity with "pseudomyotonic" bursts and spontaneous fibrillations; voluntary muscle contraction showed mild reduction

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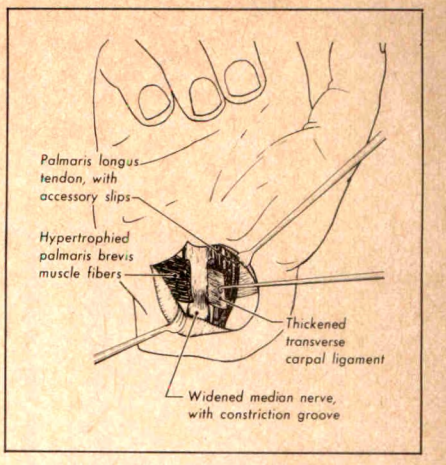
Nerve Conduction Studies			
	Normal	Preoperative	Postoperative
Conduction velocity, m/s			
Median motor nerve, elbow to wrist			
Right	>47.5	62.2	60.5
Left	>47.5	58.0	64.0
Distal latency, ms			
Median motor nerve, wrist to thenar eminence			
Right	< 3.5	6.8	4.8
Left	< 3.5	6.8	5.4
Median sensory nerve, ring finger to wrist			
Right	< 3.2	NR*	4.0
Left	< 3.2	NR	4.0

*NR indicates no recordable response.



Operative findings, right hand.

in number of motor units firing, although the individual motor units were normal in pattern. Motor conduction velocity along the median nerve from elbow to wrist was normal, whereas the time required for a stimulus at the wrist to reach the abductor pollicis brevis in the thenar eminence (median motor nerve distal latency) was greatly prolonged. Transmission time for a stimulus delivered to the index finger to reach the wrist proximal to the carpal tunnel (median nerve distal sensory latency) was so impaired as to be unrecordable. Amplitude of the muscle action potential of the abductor pollicis brevis resulting from stimulation of the motor fibers of the median nerve proximal to the carpal tunnel was abnormally low, which indicated nerve demyelination. These electrodiagnostic findings confirmed the presence of entrapment of the median nerve at the carpal tunnel (Table). Motor and sensory distal latency studies of the mother's left median nerve were normal.

Early operation was undertaken with similar findings in each hand. The transverse carpal ligaments were extremely well developed, measuring 4 to 6 mm in thickness, with a rubbery, fibrotic consistency. The palmaris longus tendon was abnormally thickened and had abnormal tendon slips that inserted into the palmar aponeurosis. The parts of the palmaris brevis muscle that arose in the transverse carpal ligament were abnormally thickened. These muscle fibers appeared to be densely woven into the ligament in such a way as to create a pseudotunnel overlying the median nerve. Both median nerves had a swollen, fusiform shape, measured 22 mm wide, and appeared to be ischemic. On the anterior surface of each nerve, just beneath the proximal edge of the thickened transverse carpal ligament, there was a constriction groove. Bilateral carpal tunnel release procedures were carried out with sectioning of the transverse ligaments and release of the abnormal tendon slips (Figure). Postoperatively, the patient has had no sensory discomfort and has retained excellent strength in both hands ten months after surgery. Five months after operation on the right wrist and two months after operation on the left wrist, electrodiagnostic studies showed improvement (Table).

COMMENT

The CTS was delineated in the 1940s as a clinical syndrome due to pressure on the median nerve within the confines of the carpal tunnel.[1,2] In contrast to many large series that describe this syndrome in adults and account for thousands of cases,[3-5] we found only 29 cases in childhood reported to date.[6-20] In a recent study of 1,215 patients, none was younger than age 16 years.[21]

The carpal tunnel is formed posteriorly by the proximal row of carpal bones, and anteriorly by the transverse carpal ligament. Coursing through this tunnel are nine tendons, their sheaths, and the median nerve. The palmaris longus tendon passes anterior to the transverse carpal ligament, but partially inserts into that structure. The palmaris brevis muscle originates from the transverse carpal ligament and extends medially to insert into the skin of the hypothenar eminence. Compression of the median nerve within the carpal tunnel creates a syndrome that affects the thumb, the index and middle fingers, and lateral side of the ring fingers, those digits having median nerve sensory innervation. Patients are regularly awakened from sleep by pain, numbness, burning, or tingling, which is gradually relieved by wringing or shaking the affected hand. Physical examination may show objective sensory deficits of the median nerve sensory distribution and Tinel's and/or Phalen's signs are often present. Median motor nerve involvement may produce early weakness of thumb abduction and opposition (abductor pollicis brevis and opponens pollicis),[5] and later, atrophy of the thenar eminence with severe functional deficits. In the majority of cases, however, objective clinical findings do not develop for months, or even years. Our patient had a typical history of nocturnal hand paresthesias, but normal results from physical examination of his hands. Accurate and early diagnosis was achieved by nerve conduction and EMG studies.

It seems generally agreed that, among adult patients, thickening of the transverse carpal ligament is neither present with nor a cause of CTS.[3,21-23] Several reports of CTS in children, however, describe significant thickening of this ligament in otherwise healthy children,[12-15] and a familial incidence of CTS associated with thickened transverse carpal ligament has been described.[12] In adults, both those with and without CTS, the transverse carpal ligament has been found to be 2.0 to 3.6 mm thick,[23] much less than the 4 to 6 mm measured in our patient. Unfortunately, we were unable to explore the possibility of a familial disorder.

Other local factors that have been reported to cause CTS in childhood include trauma,[9,10] congenital anomaly,[8] hemangioma,[24] tendon calcification,[16] mucopolysaccharidosis,[18] and mucolipidosis.[17] Taylor[5] has reviewed the many and varied causes of CTS in adults, but the majority of adult cases seem to be idiopathic. The role of occupational stresses has been postulated,[5] and it may be that weightlifting or riding a minibike served to precipitate symptoms in this boy. No evidence of systemic disease was found in our patient. Local anomalies of the palmaris longus tendon and of the origins of the palmaris brevis muscle, in addition to the impressive thickening of the transverse carpal ligament, were the basis for his problem.

After surgery, our patient's median nerve motor and sensory distal latencies improved, and the amplitude of the motor nerve action potentials increased, reflecting improved function of the distal median nerve and confirming the benefit afforded by early operative care.

Temporizing, nonsurgical treatments such as splinting and local injection of corticosteroids, often suggested for adult patients, would seem to us to have no indications in a child or adolescent when an unequivocal diagnosis of CTS has been established by electrodiagnostic studies.

References

1. Cannon BW, Love JG: Tardy median palsy; median neuritis; median thenar neuritis amenable to surgery. *Surgery* 20:210-216, 1946.
2. Brain WR, Wright AD, Wilkinson M: Spontaneous compression of both median nerves in the carpal tunnel: Six cases treated surgically. *Lancet* 1:277-282, 1947.
3. Phalen GS: The carpal tunnel syndrome: 17 years' experience in diagnosis and treatment of 654 hands. *J Bone Joint Surg Am* 48:211-228, 1966.
4. Hybbinette CH, Mannerfelt L: The carpal tunnel syndrome: A retrospective study of 400 operated patients. *Acta Orthop Scand* 46:610-620, 1975.
5. Taylor N: Special review: Carpal tunnel syndrome. *Am J Phys Med* 50:192-213, 1971.
6. Martin C, Masse P: Carpal tunnel syndrome in children. *Arch Fr Pediatr* 15:930-940, 1958.
7. Hess H, Baumann F: Familiar occurrence of bilateral carpal tunnel syndrome. *Z Orthop* 106:565-569, 1969.
8. Beatty JG: Carpal tunnel syndrome caused by an unusual congenital anomaly. *Can Med Assoc J* 84:1020, 1961.
9. McClain EJ, Wissinger HA: The acute carpal tunnel syndrome: Nine case reports. *J Trauma* 16:75-78, 1976.
10. Weiland AJ, Lister GD, Villarreal-Rios A: Volar fracture dislocations of the second and third carpometacarpal joints associated with acute carpal tunnel syndrome. *J Trauma* 16:672-675, 1976.
11. Gellis SS, Feingold M, Kelly TE: Picture of the month: Mucolipidosis III (pseudo-Hurler polydystrophy). *Am J Dis Child* 129:1059-1060, 1975.
12. Danta G: Familial carpal tunnel syndrome with onset in childhood. *J Neurol Neurosurg Psychiatry* 38:350-355, 1975.
13. Miner ME, Schimke RN: Carpal tunnel syndrome in pediatric mucopolysaccharidoses: Report of four cases. *J Neurosurg* 43:102-103, 1975.
14. de Weerdt CJ: Carpal tunnel syndrome in a four-year-old child. *Ned Tijdschr Geneeskd* 113:1942-1943, 1969.
15. McArthur RG, Hayles AB, Gomez MR, et al: Carpal tunnel syndrome and trigger finger in childhood. *Am J Dis Child* 117:463-469, 1969.
16. Hotta T, Kambera H, Sato S, et al: Case of carpal tunnel syndrome due to calcification of the flexor digitorum sublimus II in a child. *Orthop Surg* Japan 21:948-950, 1970.
17. Starreveld E, Ashenhurst EM: Bilateral carpal tunnel syndrome in childhood: A report of two sisters with mucolipidosis III (pseudo-Hurler polydystrophy). *Neurology* 25:234-238, 1975.
18. McKusick VA: *Hereditable Disorders of Connective Tissue*, ed 5. St Louis, CV Mosby Co, 1972, pp 521-686.
19. Lagos JC: Compression neuropathy in childhood. *Dev Med Child Neurol* 13:531-532, 1971.
20. Lettin AWF: Carpal tunnel syndrome in childhood: Report of a case. *J Bone Joint Surg Br* 47:556-559, 1965.
21. Yamaguchi DM, Lipscomb PR, Soule RH: Carpal tunnel syndrome. *Minn Med* 48:22-33, 1965.
22. Tanzer RC: The carpal tunnel syndrome, in Coverse JM (ed): *The Hand and Upper and Lower Extremities*. Philadelphia, WB Saunders Inc, 1964, vol 4, pp 1787-1794.
23. Tanzer RC: The carpal tunnel syndrome. *Clin Orthop* 15:171-179, 1959.
24. Kojima T, Ide Y, Marumo E, et al: Hemangioma of median nerve causing carpal tunnel syndrome. *Hand* 8:62-65, 1976.

Review

Essential Fatty Acids Revisited

Zvi Friedman, MD, FRCP(C)

Polyunsaturated fatty acids (PUFAs) are aliphatic monocarboxylic acids with two or more double bonds in any positional arrangement or geometric configuration. Those PUFAs that prevent or relieve the symptoms of dietary deficiency in humans and animals are named, therefore, the essential fatty acids (EFAs).

The EFAs are a group of naturally occurring unsaturated fatty acids of chain length 18, 20, or 22 carbon atoms and they contain between two and six methylene interrupted double bonds in cisconfiguration. The fatty acids are essential to the diet of man and all higher animals as they cannot be synthesized de novo from other lipids or from carbohydrates and amino acids. There are two fundamental EFAs, linoleic and α-linolenic acids, from which all others are derived metabolically.[1] The essentiality of the PUFAs is related to their capability to incorporate into lipids and to act as a precursor in the formation of prostaglandins.

Historically, the essentiality of dietary fat was first demonstrated in 1929 by Burr and Burr[2] who observed poor growth and skin lesions in rats raised on a fat-free diet, symptoms that could be prevented by the administration of dietary linoleic acid.

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PUFA METABOLISM

Earlier studies have established that linoleate, linolenate, oleate, and palmitoleate each serve as the initial unsaturated precursor for the biosynthesis of an independent family of PUFAs.[3] The biosynthetic pathways, as depicted in Fig 1, consist of a series of desaturation and chain elongation reactions in which there is no direct crossover between unsaturated metabolites from one sequence to the other.[3]

Although no conversions take place between the member fatty acids of different series, inhibitions and competition between fatty acids within these different series have been demonstrated. Several studies[4,5] have suggested that linoleate and linolenate compete for a common system of enzymes that elongate and desaturate the molecules to produce their higher-homologue, unsaturated derivatives. This competition can be displaced in either direction, and the acid favored in this competition is dependent on the relative dietary levels of these acids.

In addition to the competitions between the PUFAs, the more saturated dietary fatty acids also influence the PUFA content of tissues. Enhanced EFA deficiency in the presence of saturated fat has been documented.[6] On diets in which EFA content is marginal, low caloric intake and slow growth result in less severe deficiency than high intake and rapid growth. It seems that the EFAs are necessary for the proper use of the saturated fatty acids and to promote growth.[2]

METABOLISM IN EFA DEFICIENCY

Competitive feeding studies and enzymatic experiments suggest that a common enzyme may further desaturate oleate, linoleate, and linolenate. The affinity of the ω3 and ω6 acids for the enzyme system is higher than ω9 and ω7 acids (ω notation signifies the position of the first double bond numbered from the methyl terminus of the acid). Thus, under normal dietary conditions, when linoleate is included, linoleate and oleate compete for the same desaturase; and in this way, the desaturation of oleate is inhibited or blocked. This inhibition is the rate-limiting step in the biosynthesis of Δ-5,8,11-eicosatrienoic acid (20:3ω9). Conversely, when the diet is devoid of the EFA linoleate, not only is the higher homologue of linoleate, arachidonate, decreased, but the synthesis of Δ-5,8,11-eicosatrienoic acid is no longer inhibited competitively. This latter acid has been observed to increase consistently in EFA-deficient animals[7] and humans.[8]

Holman et al[9] noted that EFA deficiency resulted in a higher ratio of triene to tetraene fatty acids in several tissues of animals. A ratio of trienoic-tetraenoic fatty acids of more than 0.4 is regarded as critical evidence for EFA deficiency. Elevations of the monoenoic acids oleate and

palmitoleate also are common findings during EFA deficiency.

PUFA BIOLOGIC ACTIVITY
Role in Phospholipids

The physical properties of PUFAs differ in many ways from those of long-chain saturated fatty acids. The essential fatty acids are principally found in phospholipids, and so they have an accepted structural function in lipoproteins of cell membranes and enzymes.[10] Naturally occurring phospholipids generally exist in anisotropic liquid crystal states that determine the ultimate biological properties of membrane fluidity, ionization, and counterion binding affinity.[10-12] Variation in the acyl-chain saturation is the most common determinant of membrane fluidity in nature. Saturated acyl chains form highly ordered membranes in which fluidity is low. Conversely, phospholipids with unsaturated acyl chains form disordered membranes in which fluidity is high.

The ingestion of PUFAs by man have been shown to reduce plasma cholesterol[13] and triglyceride concentration[14] and to increase their proportion in lipoprotein lipids.[15]

Precursors of Prostaglandins and Thromboxanes

Prostaglandins are a group of naturally occurring lipids formed in most tissues from PUFA precursors by a microsomal enzyme system.[16] Prostaglandins and thromboxanes are not stored but are synthesized on demand after an appropriate stimulus, immediately released, and rapidly metabolized. Prostaglandins and thromboxanes have been implicated in numerous physiologic and pathophysiologic processes in every organ system in the human.

PUFA: ROLE IN INFANT NUTRITION AND METABOLISM
Placental Transfer and Cord Blood PUFA

Normal growth of infants is dependent on an adequate supply of essential fatty acid.[17] The human fetus, like the adult, is unable to synthesize the essential fatty acids, which must therefore be derived from the maternal circulation and pass through the placenta. Previous reports,[18,19] including ours,[20] confirmed the observations that maternal plasma lipid levels are elevated during pregnancy and that these levels are substantially higher than in the neonate. However, the relationship of maternal nutrition during pregnancy to fetal plasma lipid levels remains controversial. Hansen et al[21] found no correlation between maternal nutrition during the third trimester and serum lipid values of their infants. Churchill et al,[22] however, noted lower IQs in children whose mothers had biliary tract disease during gestation, and they speculated that this could be related to decreased availability of linoleic acid for fetal brain development. We[20] showed no change in cord plasma phospholipid, cholesterol ester, triglyceride, and free fatty acid concentrations through gestation.

Furthermore, no differences in the fatty acid composition of these lipid classes were found in cord venous and arterial plasma obtained from 32 infants at birth.[20] The fatty acid composition of cord plasma phospholipids at different gestational ages is shown in Fig 2. Their gestational age varied from 24 to 44 weeks, and all were normally grown infants. The concentration of linoleic acid in cord plasma phospholipid was less than half that of the maternal value. The lowest levels

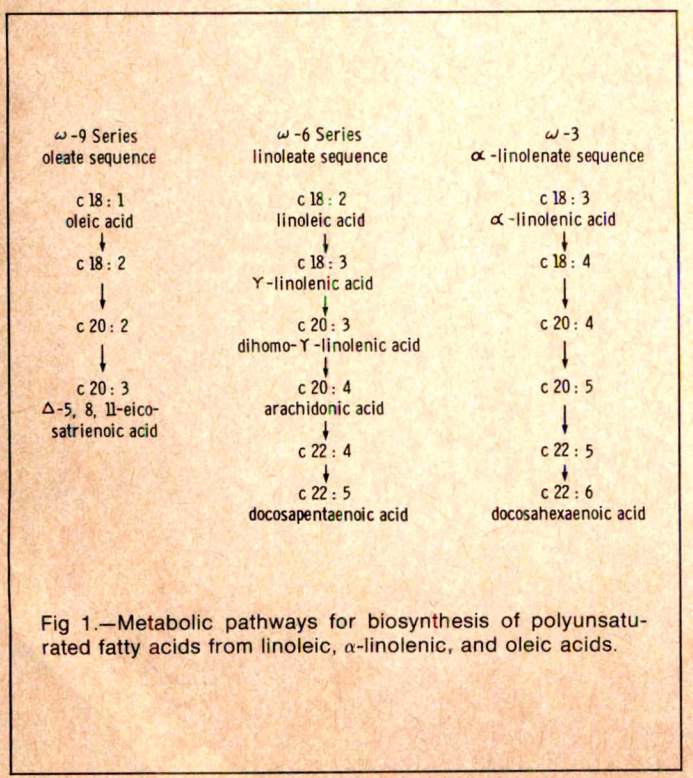

Fig 1.—Metabolic pathways for biosynthesis of polyunsaturated fatty acids from linoleic, α-linolenic, and oleic acids.

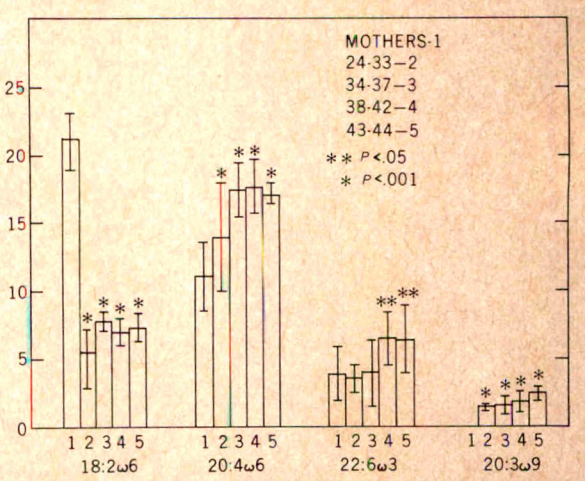

Fig 2.—Percent fatty acid composition of plasma phospholipids of mothers and their infants born at varying gestational ages. Note that relative percent of linoleic acid (18:2ω6) is lower in cord plasma phospholipids than in maternal plasma; however, levels of arachidonate (20:4ω6), docosahexaenoic acid (22:6ω3), and Δ-5,8,11-eicosatrienoic acid (20:3ω9) are higher in cord plasma than maternal plasma. Relative percent of latter acids increased with advancing gestational age. Ranges in key refer to gestational ages expressed in weeks.

of this fatty acid were noted before 34 weeks' gestation. However, venous and arterial cord plasma contained higher concentrations of the more unsaturated fatty acid, arachidonate, than did maternal plasma.[18-20] The concentration of docosahexaenoic acid, which is a homologue of the α-linolenic acid series, was noted to be higher in cord blood plasma at term as compared with maternal levels.[18-20] The increased combined total of the linoleic acid series in plasma phospholipid correlated well with the tissue levels of these fatty acids.[20]

Bruce and Svennherholm[23] reported a continuous increase in the relative concentration of fatty acids of the linoleic series in skeletal muscle phosphoglycerides, from 10% at the beginning of the second trimester of gestation to almost 50% at the age of 1 year. The increased concentration of the polyenoic fatty acids, derivatives of linoleic and α-linolenic acids, may result from the increased activity of the fetomaternal unit by preferential transfer of these fatty acids in later gestation or from enzymatic activity in the placenta or the fetus that may be responsible for desaturation and elongation of these EFAs.[24]

In the anesthetized primate, injection of labeled linoleic and palmitic fatty acids into the mother led to their rapid appearance in the fetal circulation.[25] Dancis et al[26] demonstrated the transport of free fatty acid from the maternal to the fetal side and from the fetal to the maternal side of the isolated human placenta. Selective transport of linoleic acid across the placenta was reported in the guinea pig[27]; but in this species, the fraction of linoleic acid in plasma free fatty acids is greater in the fetus than in the mother; this is contrary to the findings in the human. Fatty acid composition of adipose tissue triglycerides in the newborn infant also differs from that of the mother[28] in the same manner as that of plasma lipids. Because of the low concentration of linoleic acid in fetal adipose tissue, its contribution to fetal plasma free fatty acid composition during lipolysis is small.

The relative percentage of the fatty acid Δ-5,8,11-eicosatrienoic acid was found to be higher in cord plasma of all infants than in maternal plasma and the level seems to increase with advanced gestation (Fig 2).[18,20,29] Although this abnormal fatty acid is elevated in EFA deficiency, such a diagnosis is not certain at the time of birth since the polyenoic acids of the linoleic acid series may be higher in the newborn infant than in the mother, yet the possibility is not eliminated that the infant may have a relative lack of EFAs. Furthermore, an increased Δ-5,8,11-eicosatrienoic acid level may reflect a generalized increase in desaturation and/or elongation of fatty acid chains in the developing fetus.

Tissue PUFA Composition

Body stores of EFAs are low in low-birth-weight infants.[30] The concentration of linoleic acid in fetal tissue is less than that seen in adults,[31] and the proportion of linoleic acid in muscle phospholipids is found to increase with advancing gestational age.[23]

We have analyzed (unpublished data, December 1978) various tissue samples from 25 human fetuses and newborns for the relative concentration of the fatty acids in phospholipids, cholesterol ester, triglycerides, and free fatty acids. Their gestational ages ranged from 16 to 44 weeks. Representative tissue from kidney medulla and cortex is shown in Fig 3. No differences are observed between the levels of the individual EFAs, linoleate and arachidonate, in the different tissues beyond 16 weeks of gestation. However, the level of arachidonate in the various tissue phospholipids is considerably elevated as compared with the level of linoleic acid. Linoleate and arachidonate cord plasma values are a reflection of their tissue levels. Both show a reduced linoleate

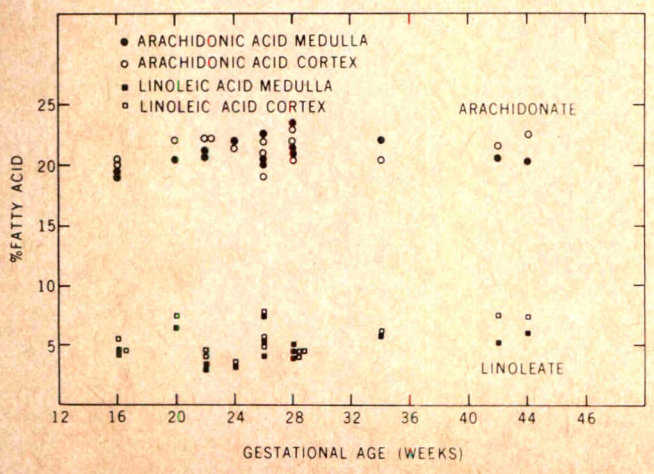

Fig 3.—Percent fatty acid composition of renal phospholipids in neonates at various gestational ages. No changes are seen between levels of linoleate and arachidonate in renal tissue beyond 16 weeks of gestation.

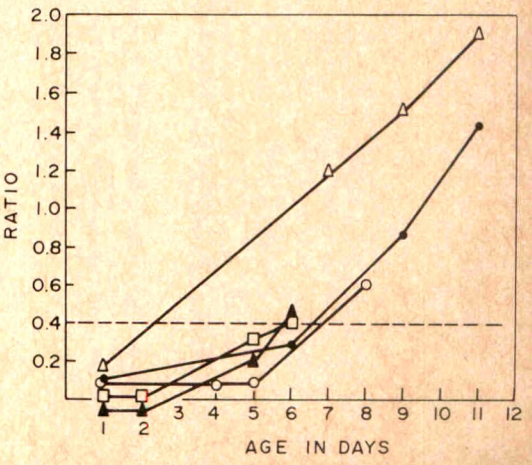

Fig 4.—Ratio of Δ-5,8,11-eicosatrienoic acid to arachidonic acid in plasma phospholipids during fat-free diet. Dotted line signifies normal ratio. Open and solid triangles, open and solid circles, and open square each represent a different neonate (from Friedman et al[29]).

level compared with the maternal level; however, the higher homologue, arachidonate, is higher than the maternal value. The low plasma concentration of linoleate reflects the reduced tissue level of this fatty acid.

This situation increases the maternal-fetal gradient for linoleic acid that may facilitate its transfer across the placenta. Tissue enrichment in arachidonic acid may play an important role by maintaining the normal function of biological membranes and by serving as a substrate for prostaglandin biosynthesis. These functions may influence fetal physiology during intrauterine development.

After birth, the diet affects the fatty acid composition of adipose tissue. In the period of rapid weight gain, during early infancy, changes in adipose tissue composition can occur in a relatively short time.[32] Recently, Widdowson et al[33] demonstrated a profound difference in the fatty acid composition of adipose tissues between British and Dutch infants in the first year of life. The differences were influenced directly by the nature of the fat in the diet.

EFA Deficiency Syndrome

Clinical Manifestations Associated With Oral Diets.—Work with experimental animals showed that the extremely young are more susceptible to EFA deficiency owing to lack of fat in the diet than are adults.[34] Similarly, body stores of EFAs are low in low-birth-weight infants, which results in the deficiency state becoming evident more rapidly than in an adult. Most of the earlier studies that have been performed on humans included infants. These studies, which started as early as 1919 by Von Gröer,[35] showed the effects of diets low in fat on growth or weight loss,[35] susceptibility to infection,[35,36] and skin eruption.[36] The observation that skin lesions in rats fed a low-fat diet were cured by the addition of fats rich in PUFAs stimulated clinical studies in infants and children with chronic eczema.[37] Their diets were supplemented with oil containing PUFAs and were noted to induce a substantial clinical improvement that was associated with increasing iodine values to the same range as for control subjects. These results were encouraging enough to warrant further studies to evaluate the role of unsaturated fatty acids in human nutrition.

Hansen et al[17] fed 428 healthy infants one of five proprietary milk mixtures adequate in protein, minerals, and vitamins but varying in linoleic acid content from 0.1% to 7.3% of the calories. Two of the milk mixtures were found to contain inadequate amounts of linoleic acid for the infant's requirements. One was low in fat (1.0% of calories), and one contained fat low in linoleic acid content. A high proportion of babies who were fed the latter two milk mixtures before 6 weeks of age and who remained on the diets for 3 months had dry, thick, desquamated skin develop and their growth was retarded. The clinical manifestations disappeared after the administration of diets that provided 1% or more of the calories as linoleic acid.

Further studies[38] demonstrated that infants do not usually show overt signs of fat deficiency until they have been receiving cow's milk formula for about two months. The clinical syndrome of linoleic acid deficiency appears as inefficient somatic growth in spite of adequate caloric intake, together with skin lesions. These manifestations showed a dramatic response to a diet containing linoleic acid.

Increased basal metabolic rate in rats with linoleic acid deficiency was documented by Wesson and Burr[39] in 1931. In infants fed diets low in linoleic acid, increased caloric consumption was reported by Adam et al.[40] In spite of the differences of 20% to 40% in caloric intake between the infants fed diets low in linoleic acids and infants fed diets supplemented with linoleic acid, weight curves were similar for the majority of infants.

Clinical Manifestations Associated With Parenteral Nutrition.—The provision of optimal nutrition for low-birth-weight infants, for infants with congenital anomalies of the gastrointestinal tract, and for those with inflammatory bowel disease remains an important problem. Recently, total parenteral nutrition (TPN) has been established as a form of therapy for these conditions.[41] The development of reliable procedures for intravenous (IV) alimentation has emphasized preparations consisting of dextrose, amino acids, minerals, and vitamins; and recently, attention has been focused on PUFAs.

Recently, Collins et al[42] described EFA deficiency induced by prolonged administration of fat-free IV infusion in a 44-year-old man. The biochemical manifestations of EFA deficiencies were accompanied by dermal symptoms. Both the clinical and biochemical changes were corrected when linoleic acid was given in the form of fat emulsions. Similar studies of infants whose conditions were maintained by long-term, fat-free parenteral nutrition demonstrated the development of clinical signs together with biochemical evidence of EFA deficiency.[43,44] The administration of diets containing linoleic acid converted these clinical and biochemical manifestations to normal.

We studied[29] five sick newborns whose conditions were maintained by fat-free IV alimentation and who had extremely rapid biochemical changes in the plasma develop that were compatible with the diagnosis of EFA deficiency during the first week of life and that were reversible with oral feedings containing EFA. The youngest and the smallest infants exhibited these changes as early as the second and third days of life (Fig 4).

The body of a premature infant weighing 1,000 g contains approximately 0.5% glycogen, 1% fat, and 8.5% protein.[30] In such an infant, the total caloric reserve is 450 calories/kg, and the nonprotein caloric reserve is only 110 calories/kg. The minimal metabolic requirement of an infant of this size is about 30 to 40 calories/kg/24 hr in the first day of life, and it increases to 45 to 50 calories/kg/24 hr thereafter. With increments for activity, stress of hypothermia or hyperthermia, asphyxia, infection, etc, the total caloric expenditure is probably in the order of 50 to 75 calories/kg/24 hr.

Because of the limited nonprotein caloric reserve, these infants must

mobilize fatty acids early for caloric needs when faced with deficient dietary intake. Thus, the borderline stores of EFA characteristic of the premature and the high caloric expenditure in these infants may contribute to the early onset of EFA deficiency that we observed among premature infants receiving fat-free parenteral feedings. Furthermore, during parenteral alimentation, the outflow of linoleic acid from adipose tissue is blocked, at least in part, by the high blood insulin levels accompanying dextrose administration. During fat-free IV alimentation, there is a correlation between EFA deficiency in plasma and that in tissues.[44] Similar correlation has not yet been demonstrated in cases with rapid onset of EFA deficiency.

Absence of EFA from the diet has been associated with a specific syndrome of deficiency in young animals and infants. For a complete description, the reader is referred to several published reports.[1,34] The syndrome includes the following: (1) diminished growth[2,17]; (2) dermatitis[2,17,44,45] (Fig 5), diminished skin pigmentation, caudal necrosis,[2] and loss of muscle tone[46]; (3) anatomical and degenerative histologic changes in the kidney,[2] lung,[47] and fatty liver[48]; and (4) physiologic changes that include impaired reproduction,[49] increased basal metabolic rate,[39,50] increased permeability of skin, impaired water balance,[39,49] increased fragility and permeability of cellular membranes associated with changes in intracellular membranes,[51,52] ECG changes,[53] lowered resistance to radiation injury,[54] and atherosclerotic changes.[55]

Effect on RBCs.—Fatty acid composition of RBC changes in relation to dietary linoleate as it does in plasma, but the changes occur more slowly. Farquhar and Aherens[56] suggested the evaluation of fatty acid composition of human RBCs to assess degrees of malabsorption in clinical disorders or adherence to a prescribed dietary regimen. However, our study[45] showed that although the fatty acid composition of RBC phospholipids of infants with EFA deficiency and at recovery follow a pattern similar to that of plasma, these changes occurred more slowly. Increased RBC osmotic fragility was reported in EFA-deficient rats.[57] However, we[45] did not demonstrate changes in RBC osmotic fragility in neonates with rapid onset of EFA deficiency.

Effect on Platelets.—Recently, the importance of arachidonic acid biotransformation in platelets has been elucidated.[51] In addition, hemorrhagic problems of unknown etiology are common in sick low-birth-weight infants.[58] Many premature infants are being given TPN, and EFA deficiency is a frequent occurrence.

Hence, we examined the rapid onset of EFA deficiency in premature infants and its possible effect on platelet function. We found[59] that the EFA-deficient infants had impaired platelet aggregation when compared with controls (Fig 6). In addition, the platelets from EFA-deficient infants demonstrated evidence of disaggregation. On recovery from their deficient state, the low-birth-weight infants had platelet functions similar to those of apparently healthy premature infants.

The relationship between the platelet dysfunction and EFA deficiency is not clear from this study. However, it is attractive to speculate on the possible connection between arachidonic acid depletion (ie, EFA deficiency) and platelet dysfunction. Thromboxane A_2, a key mediator of human platelet aggregation,[60] is formed from arachidonic acid, and the blockage of its synthesis results in abnormal platelet aggregation.[60] Decreased prostaglandin formation in vivo has been noted in EFA-deficient infants[61] and in vitro in tissues of EFA-deficient animals.[62] But in vitro platelet studies in EFA-deficient animals have shown conflicting results, perhaps because of the species differences or other possible defects that are known to be factors in platelet behavior and may contribute to hemorrhagic disorders.[63] Normal platelet phospholipid is important in the aggregation phenomenon and arachidonic acid is an important component of membrane phospholipids.[64] The EFA deficiency state may reduce the availability of arachidonic acid to the platelet.

Finally, it is not known whether or not the abnormality of platelet aggregation in those EFA-deficient patients truly reflects the plasma abnormality since the accumulation of Δ-5,8,11-eicosatrienoic acid itself depresses platelet aggregation.[65] This fatty acid is found in important amounts only in subjects with EFA deficiency. It is also not clear whether EFA deficiency leads to increased permeability and fragility of blood vessels.[66]

Effect on Prostaglandins.—Van Dorp[62] studied the prostaglandin content of various parts of the kidney medulla, in normal and EFA-deficient rabbits. These studies demonstrated that EFA deficiency in rabbits is associated with prostaglandin deficiency. It was suspected, but not proved, that in the EFA-deficient animal, there is a sharp decrease in precursor acids.[62] This hypothesis is supported by Kaa,[67] who showed increased activity of prostaglandin synthetase in vitro in EFA-deficient rats.

We[61] measured the excretion of the major urinary metabolite of prostaglandins E_1 and E_2, 7α-hydroxy-5,11-diketotetranorprostane-1,16 dioic acid (PGE-M) for three infants during EFA deficiency and at recovery from the deficiency state and for nine thriving control neonates. A significant difference between the PGE-M excretion in the group of infants with EFA deficiency before and after treatment was found ($P < .05$) (Fig 7). Significant differences ($P < .05$) in PGE-M excretion were also found between the control and EFA-deficient infants.

The biochemical evidence of EFA deficiency and the decreased levels of PGE-M excretion are rapidly corrected when patients resume a diet containing EFA. Since PGE-M is the terminal product arising from sequential 15-dehydrogenation, Δ 13 reduction and both β and ω oxidation of prostaglandins E_1 and E_2, any decrease in its excretion reflects decreased prostaglandin synthesis and turnover in the body.[68] This decrease is probably related to a decrease in the precursor EFA, although synthetase deficiency or altered prostaglandin metabolism has not been excluded. The observation that feeding arachi-

donate to humans increased the excretion of PGE-M[69] indicates that the excretion of this prostaglandin metabolite is related to the amount of arachidonic acid in the precursor lipids. Because prostaglandins and thromboxanes are not stored in tissues, PGE-M excretion usually indicates biosynthetic activity for which both prostaglandin synthetase and substrate must be present.

Effect on Pulmonary Surfactant.—Deficiency in EFA has been shown to cause a respiratory disease syndrome in chickens,[47] and in rats it resulted in a substantial reduction in palmitate content of lung surfactant.[70] Lung structure is not altered by EFA deficiency except for mitochondrial changes confined to type II cells,[52] and the alteration in lung mechanics in EFA-deficient rats resulted from impaired surfactant surface-tension-lowering activity.

Fig 5.—Infant with skin lesions during essential fatty acid deficiency (from Friedman et al[45]).

We[71] studied a low-birth-weight infant who had biochemical evidence of EFA deficiency in the plasma after suffering from chronic bronchopulmonary dysplasia and recurrent episodes of necrotizing enterocolitis. A lower than normal level of palmitic acid and an increased level of palmitoleic and oleic acids were seen in pulmonary surfactant phospholipid components. On treatment and recovery from EFA deficiency, the fatty acid pattern both in plasma and surfactant phospholipids returned to normal, along with clinical improvement in the respiratory illness. The major molecular species of phosphatidylcholine in lung tissue and lavage fluid is dipalmitoyl phosphatidylcholine.

Phosphatidylcholine is considered to play an important role in determining the surface properties of pulmonary surfactant. Reduction of this species of phosphatidylcholine results in surfactant with diminished surface-tension-lowering capacity in EFA-deficient rats.[72]

Besides phosphatidylcholine, the surfactant complex contains other highly characteristic phospholipid components. In the adult, the second major phospholipid is phosphatidylglycerol, but it has not been demonstrated in infants with hyaline membrane disease. The association between EFA deficiency and the impairment of surfactant phosphatidylcholine and phosphatidylglycerol fatty acid composition has been shown in our patient. This alteration may diminish lung function and so contribute to the pathophysiology of hyaline membrane disease, chronic bronchopulmonary dysplasia, cystic fibrosis,[73,74] and other respiratory diseases associated with inadequate nutrition, inviting an EFA deficiency.

Effect on the CNS and Retina.—The availability of long-chain PUFAs seems to be related to the degree of brain and CNS development. Linoleic and α-linolenic acids represent a small proportion of the fatty acyl components of the phosphoglycerides of fetal brain.[24] In contrast, arachidonic and docosahexaenoic acids, more unsaturated EFAs, are readily incorporated into the structural lipids of the developing brain.[24] In man, the brain undergoes an accelerated growth

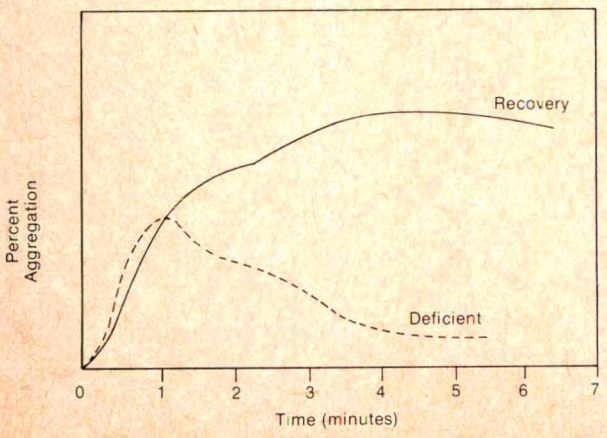

Fig 6.—Platelet aggregation patterns at 5.0 μM adenosine 5′-diphosphate during deficient period and ten days after feeding (recovery period).

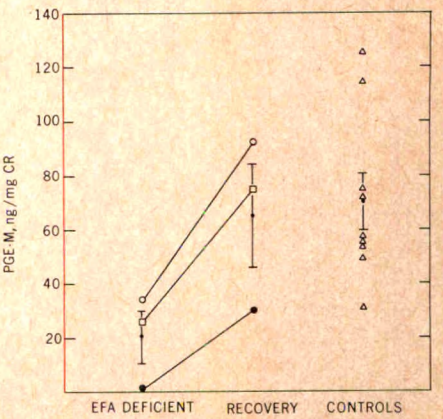

Fig 7.—Comparison of urinary excretion of 7α-hydroxy-5,11-diketotetranorprostane-1,16 dioic acid (PGE-M), expressed as ng/mg urinary creatinine (CR), for infants with essential fatty acid (EFA) deficiency and at recovery and for thriving neonates. Values expressed as mean ± SEM (from Friedman et al[61]).

phase during the last trimester of pregnancy and the first 18 months of postnatal life. During this vulnerable period, EFAs are required for structural expansion of the brain.

The effect of EFA-deficient diet during gestation, lactation, and postnatal development has been studied in the rat. Paoletti and Galli[75] reported that during fat-free diet, brain weight is decreased; total lipid and phospholipid concentrations are diminished; and the fatty acid composition of phospholipids, especially ethanolamine phosphoglyceride (which is the major highly unsaturated phospholipid constituent of brain membranes), is considerably modified. This EFA-deficient diet induces changes that involve decrease in the $\omega 6$ and $\omega 3$ fatty acids and increase in the $\omega 9$ acids. The EFA-deficient rats showed an impaired performance compared with the control, EFA-supplemented group. During the period of growth when they were returned to the control diet, the EFA-deficient rats were able to recover completely, but a permanent learning disability remained.

White et al[76] studied the brain lipids of three premature infants whose conditions were maintained by fat-free parenteral nutrition and who died. They demonstrated fatty acid alterations indicative of EFA deficiency in the two major component phospholipids of the brain, ethanolamine and choline phosphoglycerides, in the cerebrum and less so in the cerebellum. There was also a tendency toward reduction of brain phospholipid concentration in these infants.

The phospholipid composition of the retinal cells is similar to the rest of the brain. Evidence was presented[77] to show that the rate of renewal of photoreceptor membranes is dependent on the availability of dietary EFAs, and the electrical response of the photoreceptor cell membranes seems to be a function of the position of the double bond as well as a function of the total number of double bonds in fatty acid supplements.

PUFA REQUIREMENTS

The earliest estimate of the infant's requirement for linoleic acid as approximately 1% of the calories was based on clinical observations, caloric intake, and serum levels of the dienoic, trienoic, and tetraenoic acids.[40] When the means of assessing the linoleate requirement from a curve relating the triene-tetraene ratio to intake of linoleate was developed,[1] it became apparent that the requirement of infants could be deduced from this biochemical parameter as well. Extensive data relating PUFAs of human serum to intake of linoleate are presented in the classical study of Hansen et al.[17] From that study, it seems that 1% of calories is a minimum requirement and that 4% of calories is an optimal intake. The plot of the triene-tetraene ratio of serum fatty acids vs linoleate intake of infants shows that the low ratio indicative of normal EFA metabolism was reached by about 1% of calories from linoleic acid.[7] The effect of variable dosage of dietary intake of linoleic acid on the total dienes, trienes, and tetraenes of serum indicated that 1% to 2% of calories as linoleate satisfies the requirements for all the biochemical conversions of PUFA, as well as permitting normal growth and preventing dermatitis.

The potency of arachidonic acid as EFA has been shown to be greater than that of linoleic or γ-linolenic acids, but all are effective in the treatment of EFA deficiency and promote normal growth. Although the α-linolenic acid ($\omega 3$) series has been considered to be essential, it cannot fulfill all the functions of the $\omega 6$ series, and so it has been questioned as possessing true essentiality. Although tissues, the CNS tissues in particular, contain a relatively high proportion of the metabolic products of α-linolenic acids, we must await demonstration of their particular function.

SUPPLEMENTATION OF PUFA

Traditionally, linoleic acid is considered the dietary EFA, for it is the commonest fatty acid that will provide all the requirements known for PUFAs in humans and animals, and it can function alone in the diet to meet the EFA requirements.

Diets

Human Breast Milk.—The fatty acid composition of human milk has been studied in detail. The patterns of fatty acids from the two breasts were found to be similar after the same nursing, but fasting and time of day both influenced total fat and fatty acid composition of the milk.[78] Fatty acid composition of breast milk changes with the nature of the dietary fat.[79] With the trend in the American diet toward a higher proportion of unsaturated fatty acids including linoleate, there is an increase in breast milk linoleate content that can vary from 1.0% to 43.0% of total fat. However, an average content ranges from 8% to 10%. Since fat provides about 50% of the calories in human milk, it contains more than an adequate amount of the EFA linoleate.

Infant Formulas.—The American Academy of Pediatrics[80] has recently recommended that infant formulas should contain a minimum of 3.3 g of fat per 100 kcal (30% of calories) and 300 mg of linoleic acid per 100 kcal (approximately 2.7% of total calories) to provide a fat-carbohydrate ratio within a range that is customary in infant diets. The Academy was concerned that excess linoleic acid would produce peroxidation and increase the vitamin E requirement, but it did not set an upper limit on the linoleate content of the diet, noting that in some human milks the linoleic acid content is 8% to 10% of the fat. However, previous reports[79] demonstrated that the linoleic acid content in breast milk varies widely with the mother's diet.

Several of the most widely used formulas in the United States are based on cow's milk protein with added lactose. All contain vegetable oils of one type or another. The fatty acid composition and fat content of infant formulas are summarized in the Table. All the formulas contain considerably more linoleic acid than human milk lipids. The long-term effects of these dietary regimens are unknown.

Parenteral Fat Emulsion.—In the newborn infants, it is difficult to provide an optimal caloric intake in the form of amino acids and carbohydrates because excessive fluid volumes are needed when isotonic solu-

tions are used, and the glucose load provided by hypertonic solutions is frequently not tolerated. Therefore, soybean oil emulsion (Intralipid), which has a high caloric density and low osmolality, has been used increasingly to provide additional calories and EFAs.[81,82] This emulsion, like most vegetable oils, is rich in the EFA linoleate, which accounts for 54% of its fatty acid content. Several studies[81,82] documented the efficacy of the administration of Intralipid in alleviating clinical and biochemical manifestations of EFA deficiency.

Inunction of Oil.—Inunction of EFAs was found to relieve EFA deficiency in animals.[83] Cutaneous application of esters of linoleic or arachidonic acids or sunflower seed oil, a rich source of linoleic acid, reduced the elevated rate of transepidermal water loss in deficient rats,[83] whereas topically applied dinoprostone (prostaglandin E_2) effectively cured the scaly skin of EFA-deficient rats.[84] Inunction of sunflower seed oil to the forearms of patients with EFA deficiency lowered the rate of water loss, cured scaly lesions, and corrected the abnormal skin lipids[85] and restored their plasma fatty acid patterns to normal, indicating that penetration of the linoleic acid through the skin had occurred.

We[45] studied two sick newborn infants who received fat-free parenteral nutrition and had biochemical and clinical evidence of EFA deficiency. After the inunction of sunflower seed oil, these manifestations disappeared. However, it seems impossible from our studies to predict the exact amount of the absorption of linoleic acid after inunction. Even the cutaneous application of relatively large quantities used with our patients failed to replenish tissues deficient in EFA.

We recently demonstrated the ability to correct platelet dysfunction and to increase prostaglandin E biosynthesis and turnover by the inunction of sunflower seed oil to newborn infants with EFA deficiency.[61] The failure to demonstrate biochemical correction of EFA deficiency in the serum of certain infants[86] is not entirely surprising since during fat-free parenteral alimentation, the outflow of linoleic acid from adipose tissue is blocked at least in part by the high blood insulin levels accompanying dextrose administration.

Plasma.—It has been recommended[87] that the prevention and/or treatment of EFA deficiency may be provided by biweekly infusion of plasma, 10 mL/kg. However, a 1.0-kg infant requires 1 calorie of linoleic acid for each 100 calories. Fasting adult plasma has approximately 1 mg/mL of linoleic acid; thus, for each 100-calorie total intake, the infant requires about 110 mL of plasma to supply adequate linoleic acid. This would be impractical. We[29] have shown that neither two exchange transfusions performed on two sick infants on different days during the first week of life nor repeated blood transfusions could prevent or correct the rapid onset of EFA deficiency.

EXCESSIVE PUFA INTAKE

Since Burr and Burr[2] demonstrated the importance of certain fats necessary for normal growth, research on EFAs has been mainly concerned with the symptoms of EFA deficiency and the administration of the minimal EFA requirement to prevent or treat the deficiency state. However, little is known about the toxicity or adverse effects of high levels of these substances in the diet.

Toxic Effects of PUFAs

Several hazardous effects of Intralipid have been reported for the newborn infant: (1) a reduced plasma clearance rate in small-for-date infants, as well as among premature infants born before 32 weeks of gestation and during an acute illness[81,88]; (2) displacement of bilirubin from albumin binding sites and an increased risk of kernicterus in the jaundiced newborn; (3) the deposition of lipid material in macrophages that may alter immunity[89]; (4) immunosuppressive effects[90]; (5) and the potential risk of substitution of phytosterols for cholesterol in the developing CNS, which

Total Fat, Fatty Acid, and Vitamin E Composition of Human Milk, Cow's Milk, and Commercial Infant Formulas*

Diets	Source of Fat	Fat, g	% Calories From Fat	Linoleic Acid, g	Linoleic Acid, % Weight (Fat)	Linoleic Acid, % Calories	Vitamin E, IU	Ratio Vitamin E, IU to Linoleic Acid, g
Human milk[108]†	. . .	5.0	45.0	.4	8.0	3.6	.49	1.2
Whole cow's milk	. . .	4.5	40.5	0.09	2.0	0.8	0.09	1.0
Cow's milk, 2%	. . .	3.0	27.0	0.06	2.0	0.5	0.06	1.0
Skim cow's milk	. . .	Trace	. . .	. . .	. . .	. . .	. . .	. . .
Enfamil 20	Soy, coconut	5.5	49.5	2.25	41.0	20.2	1.9	0.8
Pregestimil	MCT, corn	4.1	36.9	.29	7.0	2.6	1.6	5.5
Prosobee	Soy	5.0	45.0	2.5	50.0	22.5	2.2	0.9
Similac 20	Soy, coconut	5.3	47.7	1.2	23.0	11.0	2.2	1.8
PM 60/40	Corn, coconut	5.6	50.4	1.5	26.9	13.5	2.2	1.5
Isomil	Soy, coconut	5.3	47.7	1.2	23.0	11.0	2.2	1.8
Mullsoy	Soy	5.5	49.5	2.97	54.0	26.7	1.6	0.5
Neomullsoy	Soy	5.2	46.8	2.8	54.0	25.2	1.6	0.6
SMA	Oleo, coconut, safflower, soy	5.3	47.7	.69	13.0	6.2	1.5	2.2

*Per 100 kcal. MCT indicates medium chain triglycerides.
†Linoleic acid calculated as 8% of fatty acid content.[79,108]

could lead to changes in myelin configuration and function.

We[82] studied two sick low-birth-weight infants who received TPN, including soy bean oil emulsion for the first 9 and 12 weeks of life, respectively. There was an increase in the total concentration of the plasma triglycerides and free fatty acids when these values were compared with control infants receiving infant formulas. Histological examination of the lung (Fig 8), after the administration of Intralipid, indicated numerous globules of sudanophilic material in alveolar macrophages and capillaries. Thus, it is possible that prolonged administration of this infusion may be associated with altered pulmonary gas exchange[91] and reticuloendothelial system function.

Effect on Tissue Fatty Acid Composition and Prostaglandin Biosynthesis

We[92] have measured tissue lipid composition and the excretion of PGE-M in three infants who received TPN including this soy bean oil emulsion for several weeks, and we have compared these values with control infants. Linoleic acid was incorporated into the major lipid classes of the plasma, RBCs, and tissues in the infants receiving Intralipid. Concomitant with the increase in the relative concentration of linoleate, a decrease in the higher PUFA arachidonate was apparent. This may indicate a competition for storage in tissue lipids, a balanced content of the intake of the linoleic and linolenic acids, a rapid turnover of the long-chain PUFAs, or a combination of these factors. However, the sum of the two EFAs, linoleate and arachidonate, is similar in RBCs and tissue phospholipids of control infants and those who received Intralipid.

A significant difference ($P < .05$) between the PGE-M excretion for the group of infants before and after the administration of Intralipid was found in this study. Differences in the urinary excretions were seen between the control group and the infants receiving soy bean oil emulsion. The PGE-M excretion after the administration of Intralipid was similar to that obtained from infants with EFA deficiency. The decrease in PGE-M excretion in patients receiving a high content of linoleic acid is most likely related to a decrease in the precursor EFA, arachidonate, although an inhibiting effect of linoleic acid on prostaglandin synthesis is possible.[93]

Effect on Platelet Function

Long-term administration of a diet rich in linoleate reduced the platelet aggregation in laboratory animals and man.[94] We (unpublished data, October 1978) observed that prolonged administration of Intralipid to sick newborn infants resulted in changes of the fatty acid composition of their platelets and phospholipids, and those platelets showed reduced aggregation in response to different agents known to induce platelet aggregation.

Effect on Cholesterol

Dietary cholesterol and the ratio of PUFAs to saturated fatty acids are important determinants of the plasma cholesterol concentration, and modification of these two factors may reverse hypercholesterolemia. However, studies on the effect of dietary cholesterol and PUFAs on the plasma cholesterol in infants have yielded conflicting results.[95,96] Infants fed commercial formula rich in vegetable oil failed to show differences in serum cholesterol values when compared with infants fed human or cow's milk by the age of 2 years,[97] although slightly lower cholesterol level was detected by the age of 7 to 12 years.[98] Increased consumption of PUFAs by nursing mothers resulted in an increase in the linoleic acid level in their milk and in the infants' serum, and although the cholesterol content remained unchanged in the milk, it declined in the infants' plasma.[99]

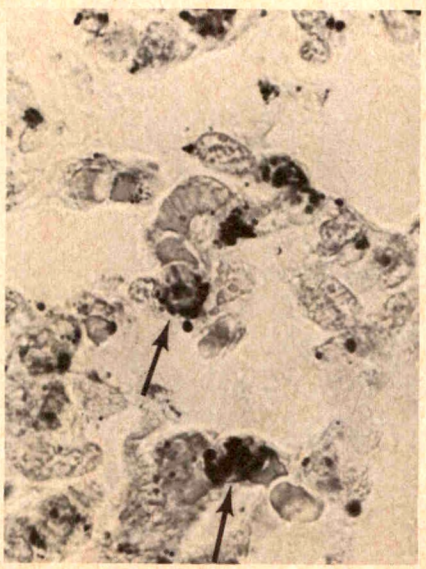

Fig 8.—Photomicrograph of lung, showing diffuse deposition of fat globules in alveolar macrophages and capillaries after administration of soy bean oil emulsion (Intralipid) (arrows) (oil red O, original magnification ×1,280) (from Friedman et al[82]).

RELATIONSHIP OF DIETARY PUFA TO VITAMINS

Vitamin E

Vitamin E seems to function primarily as an antioxidant, preventing peroxidation of membrane lipids, and as such, it contributes to the stability of the lipid structures in biological membranes. Plasma vitamin E concentration of the newborn infant is about one third that of adults, and that of the low-birth-weight infant is even lower.

A number of factors make the low-birth-weight infants more susceptible to vitamin E deficiency. These infants are born with meager stores of vitamin E and relatively small fat deposits in which the vitamin is normally stored. The capacity of the low-birth-weight infants to absorb fat and fat-soluble vitamins is limited in comparison with the full-term infant. These infants are usually fed proprietary milks in which the fat is supplied in the form of vegetable oil rich in PUFAs, particularly linoleate. It has been shown that the dietary requirement for vitamin E increases with increasing amounts of dietary PUFAs.

Although most vegetable oils with a high linoleic acid content are considered a natural source of vitamin E, it was found that vegetable oils contain a considerable amount of γ-tocopherol[100] that has only about 10% of the biological activity of α-tocopherol. Although the amounts of vitamin E usually found in formulas may be adequate to maintain normal serum tocopherol levels in term infants, these

may not be sufficient for premature infants. Thus, a relative vitamin E deficiency state may occur in these infants. In addition, these high-PUFA diets are supplemented with iron, which increase the vitamin E requirement in these low-birth-weight infants.[101]

The Committee on Nutrition of the American Academy of Pediatrics[102] recommends that the full-term infant receive 0.3 IU of vitamin E per 100 kcal and at least 0.7 IU of vitamin E per gram of linoleic acid, and it recommends that formula fed to premature infants should provide 0.7 IU of vitamin E per 100 kcal and at least 1.0 IU of vitamin E per gram of linoleic acid. In addition, the Committee recommends that the multivitamins supplement given to low-birth-weight infants should provide 5 IU of vitamin E, preferably in water-soluble form.

Pyridoxine Hydrochloride (Vitamin B_6)

The role of pyridoxine in fat metabolism and in the metabolic conversions of the EFA has been demonstrated in man and animals.[103]

PUFA INVOLVEMENT IN DISEASE STATES

Abetalipoproteinemia

The primary defect in abetalipoproteinemia is failure of synthesis of apo B, which is the major apoprotein of betalipoprotein and is also essential for the formation of prebetalipoprotein and chylomicrons.[104] The disorder usually occurs in infancy, with symptoms owing to malabsorption of fat; later, retinal and neurological abnormalities occur. Analysis of PUFAs in the plasma and RBC of these patients showed linoleic acid to be depressed and $\omega 9$ acids elevated, a patter consistent with EFA deficiency; however, a normal triene-tetraene ratio make the diagnosis of EFA deficiency state unlikely. The low level of linoleic acid may contribute to the abnormal neurological function but is unlikely to be the sole cause. Vitamin E deficiency in this condition could contribute to the deleterious effect of altered EFA metabolism on the stability and integrity of cell membrane.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is a rare disorder of infancy characterized by cessation of growth, distinct epidermal lesions, malabsorption, alopecia, dystrophy of the nails, and psychic disturbances. Aberration in the metabolism of PUFAs is considered as a factor in the pathogenesis of the disease. During exacerbations, the level of arachidonic acid in serum lipids is low, whereas linoleic acid content is higher than normal and a number of unusual unsaturated or branched fatty acids accumulate. Response to the administration of zinc chloride, diiodohydroxyquin (Diodoquin), and also parenteral fat emulsions have been reported.

Familial Deficiency of Plasma Lecithin: Cholesterol Acyltransferase

This rare disorder involves a deficiency of an enzyme that normally occurs in the plasma and transfers acyl groups, principally linoleic and arachidonic acids, from the β position of lecithin to form cholesterol ester. The principal effects include low plasma cholesteryl ester, decreased lysolecithin, deficiency in α-lipoprotein in the plasma, proteinuria, anemia, and corneal opacity. As a result of the deficient eyzyme, the plasma cholesterol ester concentration is low; and of these cholesteryl esters, the esters of saturated acids and oleic are relatively high in concentration, whereas those of linoleic and arachidonic acids are reduced. Transfusion of normal plasma containing the enzyme corrects the biochemical abnormalities.

Cystic Fibrosis

Abnormal fatty acid composition of various tissues and blood-lipid fractions has been described in patients with this disease and is characterized by a low level of linoleic acid and usually a concomitant elevation of palmitic, palmitoleic, and oleic acids.[75,105,106] The clinical course of cystic fibrosis is favorably influenced by regular IV infusions of oil emulsions rich in linoleate.[107] On the basis of these findings, it has been suggested that a defect in fatty acid metabolism in cystic fibrosis might contribute to the clinical manifestation of this disorder.[73] However, when fatty acid composition of the various plasma-lipid fractions from patients with cystic fibrosis with and without pancreatic insufficiency, from obligate heterozygous subjects, and from normal subjects was determined, only the patients with cystic fibrosis with pancreatic insufficiency had substantially abnormal fatty acid composition.[106] Vitamin E deficiency and possible altered prostaglandin biosynthesis[107] may contribute to the pathophysiology of cystic fibrosis.

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Nonproprietary Name and Trademark of Drug

Dinoprostone—*Prostin* E_2.

References

1. Holman RT: Biological activities of and requirements for polyunsaturated acids, in Holman RT (ed): *Progress in the Chemistry of Fats and Other Lipids.* Oxford, England, Pergamon Press, 1971, vol 4, pp 607-682.

2. Burr GO, Burr MM: A new deficiency disease produced by the rigid exclusion of fat from the diet. *J Biol Chem* 82:345-367, 1929.

3. Sprecher H: Biosynthesis of polyunsaturated fatty acids and its regulation, in Kunau WH, Holman RT (eds): *Polyunsaturated Fatty Acids.* Champaign, Ill, American Oil Chemists' Society, 1977, pp 1-18.

4. Mohrhauer H, Holman RT: Effect of linolenic acid upon the metabolism of linoleic acid. *J Nutr* 81:67-74, 1963.

5. Holman RT, Mohrhauer H: A hypothesis involving competitive inhibitors in the metabolism of polyunsaturated fatty acids. *Acta Chem Scand* 17:583-590, 1963.

6. Pfifer JJ, Holman RT: Effect of saturated fat upon EFA metabolism of the rat. *J Nutr* 68:155-168, 1959.

7. Holman RT: The ratio of trienoic tetraenoic acids in tissue lipids as a measure of essential fatty acid requirement. *J Nutr* 70:405-410, 1960.

8. Hansen AE, Stewart RA, Hughes G, et al: The relation of linoleic acid to infant feeding. *Acta Paediatr Scand* 51(suppl 137):5-41, 1962.

9. Holman RT, Caster WO, Wiese HF: The essential fatty acid requirement of infants and the assessment of their dietary intake of linoleate by serum fatty acid analysis. *Am J Clin Nutr* 14:70-75, 1964.

10. Farias RN, Trucco RE: Membrane structure and function with different lipid-supplemented diets, in Bazan NG, Brenner RR, Giusto NM (eds): *Function and Biosynthesis of Lipids.* New York, Plenum Press Inc, 1977, pp 591-607.

11. Cornwell DG, Patil GS: Surface chemistry and the physical properties of polyunsaturated fatty acid containing lipids, in Kunau WH, Holman RT (eds): *Polyunsaturated Fatty Acids.* Champaign, Ill, American Oil Chemists' Society, 1977, pp 105-137.

12. Baldassare JJ, Rhinehart KB, Silbert DF: Modification of membrane lipid: Physical properties in relation to fatty acid structure. *Biochemistry* 15:2986-2994, 1976.

13. Keys A, Anderson JT, Grande F: Serum-cholesterol response to dietary fat. *Lancet* 1:787, 1957.

14. Grundy SM: Effects of polyunsaturated fats on lipid metabolism in patients with hypertriglyceridemia. *J Clin Invest* 55:269-282, 1975.

15. Morrisett JD, Pownall HJ, Jackson RL, et al: Effects of polyunsaturated and saturated fat diets on the chemical composition and thermotropic properties of human plasma lipoproteins, in Kunau WH, Holman RT (eds): *Polyunsaturated Fatty Acids*, Champaign, Ill, American Oil Chemists' Society, 1977, pp 139-161.

16. Van Dorp DA, Beerthuis RK, Nugteren DH, et al: The biosynthesis of prostaglandins. *Biochim Biophys Acta* 90:204-207, 1964.

17. Hansen AE, Wiese HF, Boelsche AN, et al: Role of linoleic acid in infant nutrition: Clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. *Pediatrics* 31:171-192, 1963.

18. Olegard R, Svennerholm L: Fatty acid composition of plasma and red cell phosphoglycerides in full term infants and their mothers. *Acta Paediatr Scand* 59:637-647, 1970.

19. Robertson AF, Sprecher H: A review of human placental lipid metabolism and transport. *Acta Paediatr Scand* 183(suppl):2-18, 1968.

20. Friedman Z, Danon A, Lamberth EL, et al: Cord blood fatty acid composition in infants and in their mothers during the third trimester. *J Pediatr* 92:461-466, 1978.

21. Hansen AE, Wiese HF, Adam DJD, et al: Influence of diet on blood serum lipids in pregnant women and newborn infants. *Am J Clin Nutr* 15:11-19, 1964.

22. Churchill JA, Ayers MA, Caldwell DF: Intelligence of children whose mothers have biliary tract disease. *JAMA* 201:482-484, 1967.

23. Bruce A, Svennherholm L: Skeletal muscle lipids: I. Changes in fatty acid composition of lecithin in man during growth. *Biochim Biophys Acta* 239:393-400, 1971.

24. Crawford MA, Hassam AG, Williams G: Essential fatty acids and fetal brain growth. *Lancet* 1:452-453, 1976.

25. Portman OW, Berhrman RE, Soltys P: Transfer of free fatty acids across the primate placenta. *Am J Physiol* 216:143-147, 1969.

26. Dancis J, Jansen V, Kayden HF, et al: Transfer across perfused human placenta: II. Free fatty acids. *Pediatr Res* 7:192-197, 1973.

27. Hershfield MS, Nemeth AM: Placental transport of free palmitic and linoleic acids in the guinea pig. *J Lipid Res* 9:460-468, 1968.

28. King KC, Arlam PAJ, Laskowski DE, et al: Sources of fatty acids in the newborn. *Pediatrics* 47:192-198, 1971.

29. Friedman Z, Danon A, Stahlman MT, et al: Rapid onset of essential fatty acid deficiency in the newborn. *Pediatrics* 58:640-649, 1976.

30. Widdowson EM: Growth and composition of the fetus and newborn, in Assalin NS (ed): *Biology of Gestation: II. The Fetus and Neonate*. New York, Academic Press Inc, 1968.

31. Roux JF, Takeda Y, Grigorian A: Lipid concentration and composition in human fetal tissue during development. *Pediatrics* 48:540-546, 1971.

32. Sweeney MJ, Etteldorf JN, Throop LJ, et al: Diet and fatty acid distribution in subcutaneous fat and in the cholesterol-triglycerides fraction of serum of young infants. *J Clin Invest* 42:1-9, 1963.

33. Widdowson EM, Dauncey MJ, Gairdner DMT, et al: Body fat of British and Dutch infants. *Br Med J* 1:653-655, 1975.

34. Soderhjelm L, Wiese HF, Holman RT: The role of polyunsaturated acids in human nutrition and metabolism, in Holman RD (ed): *Progress in the Chemistry of Fats and Other Lipids*. New York, Pergamon Press, 1970, vol 9, pp 555-585.

35. Von Gröer F: Zur frage der prakitischen bedeutung des nahr wertbegriffes nebsteinigen bemerkungen uber das fett minimum des menschlichen saulings. *Biochem Z* 97:311-329, 1919.

36. Hansen AE, Wiese HF: Clinical and blood lipid studies in a child with chylous ascites. Proceedings of the American Pediatric Society. *Am J Dis Child* 68:351-352, 1944.

37. Hansen AE: Serum lipid changes and therapeutic effects of various oils in infantile eczema. *Proc Soc Exp Biol Med* 31:160-161, 1933.

38. Hepner R: Balances of fatty acids in infant nutrition. *Current Ther Res* 9(suppl):140-148, 1967.

39. Wesson LG, Burr GO: The metabolic rate and respiratory quotients of rats on a fat-deficient diet. *J Biol Chem* 91:525-539, 1931.

40. Adam DJD, Hansen AE, Wiese HF: Essential fatty acids in infant nutrition. *J Nutr* 66:555-564, 1958.

41. Coran AG: The long-term total intravenous feedings of infants using peripheral veins. *J Pediatr Surg* 8:801-807, 1973.

42. Collins FD, Sinclair AJ, Royle JP, et al: Plasma lipids in human linoleic acid deficiency *Nutr Metab* 13:150-167, 1971.

43. Pensler L, Whitten C, Paulsrud J, et al: Serum fatty acid changes during fat free intravenous therapy. *J Pediatr* 78:1067, 1971.

44. Caldwell MD, Jonsson HT, Othersen HB Jr: Essential fatty acid deficiency in an infant receiving prolonged parenteral alimentation. *J Pediatr* 81:894-898, 1972.

45. Friedman Z, Shochat SJ, Maisels MJ, et al: Correction of essential fatty acid deficiency in newborn infants by cutaneous application of sunflower-seed oil. *Pediatrics* 58:650-654, 1976.

46. Burr GO, Burr MM, Miller ES: On the fatty acids essential in nutrition. III. *J Biol Chem* 97:1-9, 1932.

47. Hopkins DT, Witter RL, Nesheim MC: A respiratory disease syndrome in chickens fed essential fatty acid deficient diets. *Proc Soc Exp Biol Med* 114:82-86, 1963.

48. Alfin-Slater RB, Aftergood L, Wells AF, et al: The effect of essential fatty acid deficiency on the distribution of endogenous cholesterol in the plasma and liver of the rat. *Arch Biochem Biophys* 52:180-185, 1954.

49. Burr GO, Burr MM: On the nature and role of the fatty acids essential in nutrition. *J Biol Chem* 86:587-621, 1930.

50. Panos TC, Finerty JC, Wall RL: Increased metabolism in fat deficiency: Relation to dietary fat. *Proc Soc Exp Biol Med* 93:581-584, 1956.

51. Levine E, Johnson RM, Albert S: Mitochondrial changes associated with essential fatty acid deficiency in rats. *J Biol Chem* 228:15-21, 1957.

52. Edmonds RH, Beeler DA, Trebler DH, et al: Morphological alterations in type II alveolar cells in essential fatty acid deficiency. *Exp Mol Pathol* 23:276-283, 1975.

53. Caster WO, Ahn P: Electrocardiographic notching in rats deficient in essential fatty acids. *Science* 139:1213, 1963.

54. Cheng ALS, Kryder GD, Berquist L, et al: The effects of fat level of the diet on general nutrition: IX. The relationship of radiation injury in the rat to the fat content of the diet. *J Nutr* 48:161-182, 1952.

55. Morin RJ, Bernick S, Alfin-Slater RB: Effects of essential fatty acid deficiency and supplementation on atheroma formation and regression. *J Atheroscler Res* 4:387-396, 1964.

56. Farquhar JW, Aherens EH: Effects of dietary fats on human erythrocyte fatty patterns. *J Clin Invest* 42:675-685, 1963.

57. Macmillan AL, Sinclair HM: Essential fatty acids. London, Butterworth Inc, 1958, p 208.

58. Valdes-Dapena MA, Arey JB: The course of neonatal mortality: An analysis of 501 autopsies on newborn infants. *J Pediatr* 77:366-375, 1970.

59. Friedman Z, Lamberth EL Jr, Stahlman MT, et al: Platelet dysfunction in the neonate with essential fatty acid deficiency. *J Pediatr* 90:439-443, 1977.

60. Hamberg M, Svensson J, Samuelsson B: Prostaglandin endoperoxides: A new concept concerning the mode of action and release of prostaglandins. *Proc Natl Acad Sci USA* 71:3824-3828, 1974.

61. Friedman Z, Seyberth H, Lambert EL, et al: Decreased prostaglandin E turnover in infants with essential fatty acid deficiency. *Pediatr Res* 12:711-714, 1978.

62. Van Dorp DA: Recent developments in the biosynthesis and the analyses of prostaglandins. *Ann NY Acad Sci* 180:181-199, 1971.

63. Vincent JE, Melai A, Bonta IL: Comparison of the effects of prostaglandin E_1 on platelet aggregation in normal and essential fatty acid deficient rats. *Prostaglandins* 5:369-373, 1974.

64. Safrit HF, Weiss HF, Phillips GB: The phospholipid and fatty acid composition of platelets in patients with primary defects of platelet function. *Lipids* 7:60-67, 1972.

65. Silver MJ, Smith JB, Ingerman CM, et al: Arachidonic acid induced human platelet aggregation and prostaglandin formation. *Prostaglandins* 4:863-875, 1973.

66. Kramar J, Levine VE: Influence of fats and fatty acids on the capillaries. *J Nutr* 50:149-160, 1953.

67. Kaa E: In vitro biosynthesis of prostaglandin E_2 by kidney medulla of essential fatty acid deficient rats. *Lipids* 11:693-696, 1976.

68. Hamberg M, Samuelsson B: On the metabolism of prostaglandin E_1 and E_2 in man. *J Biol Chem* 246:6713-6721, 1971.

69. Seyberth HW, Oelz O, Kennedy T, et al: Increased arachidonate in lipids after administration to man: Effects on prostaglandin biosynthesis. *Clin Pharmacol Ther* 18:521-529, 1975.

70. Kyriakides EC, Beeler DA, Edmonds RH, et al: Alterations in phosphatidylcholine species and their reversal in pulmonary surfactant during essential fatty acid deficiency. *Biochim Biophys Acta* 431:399-407, 1976.

71. Friedman Z, Rosenberg A: Abnormal lung surfactant related to essential fatty acid deficiency in a neonate. *Pediatrics* 63:855-859, 1979.

72. Burnell JM, Kyriakides EC, Edmonds RH, et al: The relationship of fatty acid composition and surface activity of lung extracts. *Respir Physiol* 32:195-206, 1978.

73. Rivers JPW, Hassam AG: Defective essential fatty acid metabolism in cystic fibrosis. *Lancet* 2:642-643, 1975.

74. Sanjurjo P, Allue X, Rodriquez-Soriano J: Fatty acid composition of lecithin fraction of mucus in cystic fibrosis. *Lancet* 1:572, 1977.

75. Paoletti R, Galli C: Effects of essential fatty acid deficiency on the central nervous system in the growing rat, in Elliott K, Knight J (eds): *Lipids, Malnutrition, and the Developing Brain*. Ciba Foundation Symposium. Amsterdam, Excerpta Medica, 1972, pp 121-132.

76. White HB Jr, Turner MD, Turner AC, et al: Essential fatty acid deficiency in brain lipids of three premature infants receiving intravenous fat-free administration, in Meng HC, Wilmore DW (eds): *Fat Emulsion in Parenteral Nutrition*. Chicago, American Medical Association, 1976, pp 31-35.

77. Wheeler TG, Benolken RM, Anderson RE: Visual membranes: Specificity of fatty acid pre-

cursors for the electrical response to illumination. *Science* 188:1313-1314, 1975.

78. Wilson BF III, Canolty NL, Aitchison JM, et al: Effects of sampling and dietary fat on gross and fatty acid composition of human milk. *Nutr Rep Int* 17:63-70, 1978.

79. Jensen RG, Hagerty MM, McMahon KE: Lipids of human milk and infant formulas: A review. *Am J Clin Nutr* 31:990-1016, 1978.

80. Committee on Nutrition, American Academy of Pediatrics: Commentary on breast-feeding and infant formulas including proposed standards for formulas. *Pediatrics* 57:278-285, 1976.

81. Gustafson A, Kjellmer I, Olegard R, et al: Nutrition in low-birth-weight infants: I. Intravenous injection of fat emulsion. *Acta Paediatr Scand* 61:149-158, 1972.

82. Friedman Z, Marks KH, Maisels MJ, et al: The effect of parenteral fat emulsion on the pulmonary and reticuloendothelial systems in the newborn infant. *Pediatrics* 61:694-698, 1978.

83. Van Dorp DA: Essential fatty acids and prostaglandins, in *Twenty-fourth International Congress of Pure and Applied Chemistry*. London, Butterworth & Co, 1974, vol 2, p 117.

84. Ziboh VA, Hsia SL: Effects of prostaglandin E_2 on rat skin: Inhibition of sterol ester biosynthesis and clearing of scaly lesions in essential fatty acid deficiency. *J Lipid Res* 13:458-467, 1972.

85. Press M, Hartop PJ, Prottey C: Correction of essential fatty-acid deficiency in man by the cutaneous application of sunflower-seed oil. *Lancet* 1:597-599, 1974.

86. Hunt CE, Engel RR, Modler S, et al: Essential fatty acid deficiency in neonates: Inability to reverse deficiency to topical applications of EFA rich oil. *J Pediatr* 92:603-607, 1978.

87. Filler RM, Eraklis AJ, Rubin VG, et al: Long-term parenteral nutrition in infants. *N Engl J Med* 281:589-594, 1969.

88. Bryan H, Shennan A, Griffin E, et al: Intralipid: Its rational use in parenteral nutrition of the newborn. *Pediatrics* 58:787-790, 1976.

89. Passwell JH, David R, Katznelson D, et al: Pigment deposition in the reticuloendothelial system after fat emulsion infusion. *Arch Dis Child* 51:366-367, 1976.

90. McCormick JH, Neill WA, Sim AK: Immunosuppressive effect of linoleic acid. *Lancet* 2:508, 1977.

91. Greene HL, Hazlett D, Demaree R: Relationship between Intralipid-induced hyperlipemia and pulmonary function. *Am J Clin Nutr* 29:127-135, 1976.

92. Friedman Z, Frolich JC: Essential fatty acids and the major urinary metabolites of the E prostaglandins in thriving neonates and in infants receiving parenteral fat emulsions. *Pediatr Res* 13:932-936, 1979.

93. Pace-Asciak C, Wolfe LS: Inhibition of prostaglandin synthesis by oleic, linoleic and linolenic acids. *Biochim Biophys Acta* 152:784-787, 1968.

94. Hornstra G, Lewis B, Chait A, et al: Influence of dietary fat on platelet function in men. *Lancet* 1:1155-1157, 1973.

95. Sweeney MJ, Etteldorf JN, Dibbons WT, et al: Dietary fat and concentrations of lipid in the serum during the first 6 to 8 weeks of life. *Pediatrics* 27:765-771, 1961.

96. Darmady JM, Fosbrooke AS, Lloyd JK: Prospective study of serum cholesterol levels during first year of life. *Br Med J* 2:685-688, 1972.

97. Glueck CJ, Tsang R, Balistreri W, et al: Plasma and dietary cholesterol in infancy: Effects of early low or moderate dietary cholesterol intake on subsequent response to increased dietary cholesterol. *Metabolism* 21:1181-1192, 1972.

98. Hodgson PA, Ellefson RD, Elveback LR, et al: Comparison of serum cholesterol in children fed high, moderate or low cholesterol milk diets during neonatal period. *Metabolism* 25:739-746, 1976.

99. Potter JM, Nestel PJ: The effects of dietary fatty acids and cholesterol on the milk lipids of lactating women and the plasma cholesterol of breast fed infants. *Am J Clin Nutr* 29:54-60, 1976.

100. Bieri JG, Poukka Evarts R: Tocopherols and fatty acids in American diets. *J Am Diet Assoc* 62:147-151, 1973.

101. Williams ML, Shott RG, O'Neal PL, et al: Role of dietary iron and fat on vitamin E deficiency anemia of infancy. *N Engl J Med* 292:887-890, 1975.

102. Committee on Nutrition, American Academy of Pediatrics: Nutritional needs of low-birth-weight infants. *Pediatrics* 60:619-630, 1977.

103. Mueller JF, Iacono JM: Effect of desoxypyridoxine-induced vitamin B_6 deficiency on polyunsaturated fatty acid metabolism in human beings. *Am J Clin Nutr* 12:358-367, 1963.

104. Gotto AM, Levy RI, John K, et al: On the protein defect in abetalipoproteinaemia. *N Engl J Med* 284:813-818, 1971.

105. Underwood BA, Denning CR, Navab M: Polyunsaturated fatty acids and tocopherol levels in patients with cystic fibrosis. *Ann NY Acad Sci* 203:237-247, 1972.

106. Hubbard VS, Dunn GD, Di Sant 'Agnese PA: Abnormal fatty acid composition of plasma lipid in cystic fibrosis: A primary or a secondary defect? *Lancet* 2:1302-1304, 1977.

107. Elliott RB: A therapeutic trial of fatty acid supplementation in cystic fibrosis. *Pediatrics* 57:474-479, 1976.

108. Fomon SJ: *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974, p 359.

Essay

Hyperactivity

Symptom Complex or Complex Symptom?

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• The phenomenon of "hyperactivity" is well recognized. Results of long-term follow-up studies show that children diagnosed as "hyperactive" are at risk for severe problems during adolescence and adulthood. However, no common diagnostic criteria exist for "hyperactivity." The term can refer to a number of very different behaviors, and children diagnosed as "hyperactive" may also exhibit one or more concomitant difficulties. A "hyperactive" child should be carefully assessed to determine the nature of the behavioral problem and its source, and the term "hyperactivity" itself should be used with caution.

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Professionals from a multitude of disciplines continue to be perplexed about the enigma called "hyperactivity." Its clinical phenomenology is well recognized: there exist a group of children who have trouble directing their attention and activity. They are likely to encounter difficulty in the classroom, on the playground, in the neighborhood, and at home. Often they exasperate themselves, their siblings, their peers, and the adults in their lives. Although the clinical picture is familiar, some fundamental questions remain. Is there a genuine homogeneity to this group? Does the clinical picture in fact describe a syndrome? Does there exist commonality with regard to etiology, pathogenesis, prognosis, and management? What becomes of these children as adults? Are there predictable consequences and sequelae of growing up hyperactive?

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LONG-TERM FOLLOW-UP

An article published in the *Archives of General Psychiatry*[1] reported a prospective study of 75 hyperactive children who were followed up for ten years. They were seen initially in the Psychiatry Clinic at the Montreal Children's Hospital between the ages of 6 and 12 years. Some had received medications as part of their management (including chlorpromazine and/or amphetamines, but no methylphenidate hydrochloride). The patients as young adults were reevaluated, with a full psychiatric assessment and a review of historical data. They were compared with a control group. The former had a higher prevalence of certain traits, including impulsivity and "immature dependency." There were several common biographical characteristics: (1) The hyperactive group had had more changes of residence, had had fewer years of education than controls, and had received lower grades in high school. (2) The hyperactive group had a higher school dropout and expulsion rate. (3) More hyperactive than control subjects had been seen in court. (4) There was also a much higher percent of hyperactive subjects who had been using nonmedical drugs during the year prior to follow-up. An important finding was a higher occurrence of automobile accidents among the hyperactive subjects.

This study by Weiss et al[1] is consistent with several previous retrospective and follow-up reports, which suggest that those youngsters who are identified as "hyperactive" are at risk for a wide range of problematic adolescent and adult outcomes.[2,3] It is noteworthy that these sequelae impinge on areas beyond those linked to formal classroom preparation. Automobile accidents, difficulty with the law, drug and alcohol abuse, and other forms of life instability may be common phenomena.[4] This has significant implications for pediatrics; for at times there is a tendency to relegate school dysfunction to the educational sector, which suggests that they are purely learning problems. The growing body of evidence of a broad impact

of such dysfunctions in later life suggests that appropriate diagnosis and management is a critical part of preventive pediatrics.[5]

SAMPLE SELECTION CRITERIA

In conducting their prospective study, Weiss et al made an assumption that commonly haunts most investigations of "hyperactivity," namely, that they were studying a more or less discrete clinical entity. They used five selection criteria for "hyperactivity":

(1) Restlessness and poor concentration were their main complaints, and had been present since the earliest years. (2) The complaints were a major source of problems both at home and at school. (3) All children had IQs above 85. (4) None of the children were psychotic, borderline psychotic, epileptic, or had cerebral palsy. (5) All children were living at home with at least one parent.

It seems that the major selection criteria concerned chronic restlessness and poor concentration both at home and in schoool.

Other studies of "hyperactivity" have emphasized different traits (Table 1). There exists no clinical or investigative consensus. Therefore, it is possible, and in fact likely, that various investigators may be scrutinizing populations of children who are called "hyperactive," but who are in fact very different from each other.[5,19-22] Research of such youngsters in a learning disabilities clinic may involve a population that differs from a sample drawn from a psychiatry clinic, a public school, or a private pediatric practice.[22,23]

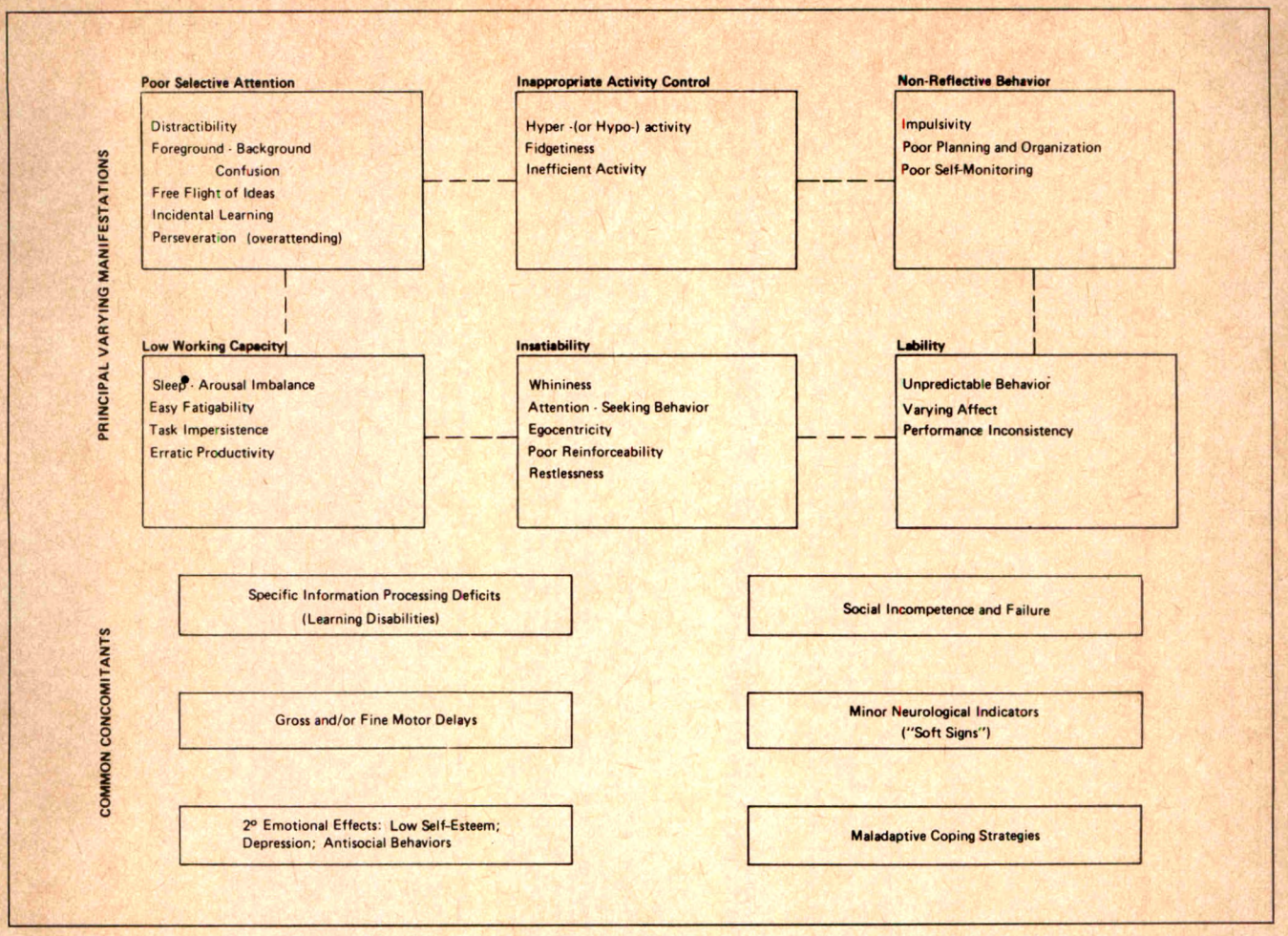
INDIVIDUAL TRAITS

The Figure depicts six basic categories of symptomatology that have been commonly reported in children said to be "hyperactive." Not all youngsters who are suspected of "hyperactivity" manifest all of these symptoms. Within a population of such patients, there is likely to be considerable heterogeneity with regard to the "penetrance" of individual traits. Moreover, any one symptom in itself suggests a differential diagnosis that goes beyond "hyperactivity" on a neurological or constitutional basis. For example, many of these symptoms also can be manifestations of childhood depression or of anxiety[24]; others may be acquired behaviors induced by the social or family milieu. Some children are impulsive during cognitive tasks because of problems with short-term memory; they need to perform before they forget what they were setting out to do. A child can become chronically inattentive because of a specific information-processing problem.[25] Thus, a youngster with a receptive language disability may become secondarily fidgety, easily distracted, and poorly focused.

Some of the traits summarized in the Figure may have existed from the

Table 1.—Admission Criteria Used in Recent Studies of Hyperactivity

Study	Symptoms Emphasized	Other Diagnostic Criteria
Bugental et al[6]	Group 1: "Behavior or attention problems"; already receiving methylphenidate Group 2: Rated high on hyperactivity dimension of Conners' Teacher Rating Scale[7]	Group 1: No information given about diagnostic criteria Group 2: No data for scores on Teacher Rating Scale; 4 of 32 children had severe learning problems
Coleman[8]	Increased activity, low frustration tolerance, impulsivity, short attention span with easy distractibility, difficulty in large groups	No information regarding specific admission criteria or sources of data for described behaviors; no school data
Conners et al[9]	Severe overactivity, short attention span, distractibility, poor frustration tolerance, disruptive behavior, failure to progress at school at rate expected on basis of potential	Intelligence quotient ≥ 80; also to have one or more of 7 listed indicators of minimal brain dysfunction, parent and teacher report, clinical evaluation
Greenberg et al[10]	Hyperactivity, impulsivity, poor attention span, poor academic performance	Diagnosis already made by referral agencies and confirmed by authors; criteria not mentioned
Greenhill et al[11]	Hyperactivity, aggressiveness, poor attention span, neurological soft-signs, antisocial behavior	Parent report and Conners' Parent Questionnaire;[12] no school data
Harvey and Marsh[13]	"Well above average" levels of activity, short attention span in learning tasks, distractibility, lack of impulse control, impaired social relationships	Normal intelligence; no school data; criteria not mentioned
Rapoport et al[14]	Persistent distractibility or motor restlessness and impulsivity	Diagnosis made by referral sources; no school data. Intelligence quotient ≥ 80; middle class
Satterfield et al[15]	Hyperactivity and distractibility plus at least 6 of 28 symptoms "found to be characteristic of the syndrome"	Criteria of Stewart et al[16] males only Intelligence quotient ≥ 80; no school data
Schain and Reynard[17]	Short attention span, restlessness, distractibility, impulsivity	Symptoms noted by referral sources; criteria not mentioned; no school data
Stewart et al[18]	Overactivity, short attention span	Symptoms described by mother; no school data



Individual traits that have been described in children with "hyperactivity."

earliest weeks of life.[26,27] In other instances, however, such manifestations may await the provocative rigors of school.[17,28] In addition, the symptoms may be situation-specific and not be evident in every setting.[29]

Many authors have believed that poor selective attention is the most pervasive common denominator in the population.[30-33] The American Psychiatric Association lists a diagnosis of Primary Attentional Disorder.[34] Problems with selective attention are likely to find expression in high levels of distractibility,[35] confusion over foreground and background (either visual or auditory, or both),[36] a tendency toward the free flight of ideas (ie, free association and daydreaming), and a propensity for incidental learning.[23] The latter involves the indiscriminate absorption of a great deal of irrelevant information, without learning in a focused manner at the right time and in the right place.

The term "hyperactivity" suggests increased motor output. Recently, however, there has been a growing awareness of "hypoactive-hyperactive" children.[34] These youngsters are distractible, impulsive, poorly organized, yet underactive. Paradoxically, some children with "hyperactivity" may exhibit appropriate *quantities* of activity.[38] What is clear is that we need to consider the *quality*, or goal-directedness, of activity rather than its overall amount.[28,39] Many of these children are not energy efficient. Their activity is misdirected, purposeless, fidgety, and seemingly random. This is an important distinction, since there exist youngsters who are restless and overactive, but purposeful and selective.[40] Such efficient children should not be confused with "hyperactive" youngsters.

It has been reported that children with "hyperactivity" seldom are reflective.[28,30,31,41] They tend to be chronically impulsive.[32] This may be seen in their overall behavior, in their social interactions, and in their efforts at problem solving. They tend not to reflect, plan, organize, or monitor their own productions. Many such youngsters feel very much out of control. Their impulsivity is constantly getting them into trouble. Often they seem not to believe what they have done, feeling unaccountable for their unpremeditated acts because things seem to happen so fast.

Many of these children seem incapable of sustained work effort. They fatigue easily doing cognitive tasks and have difficulty sustaining attention.[42] They may have problems in enduring requisite delays of gratification to achieve work.[43] They may be impersistent and inconsistent, and show fluctuating levels of arousal and

alertness. Some authors have suggested that these children are "underaroused,"[44] that they are engaged in a constant struggle to thwart fatigue. They may have as much difficulty sleeping at night[5,43] as they have in remaining alert during the day. In such cases, stimulant medication may serve to enhance arousal, alertness, and ultimately productivity.

Insatiability is a trait that has been associated with poor selective attention. Children so affected seem to be chronically restless, need to be the center of attention, often are whiny and dissatisfied, and act excessively egocentric.[32] They may respond poorly to either positive or negative reinforcement, and are therefore relatively insensitive to punishment. The value of rewards is likely to be transitory, seeming only to whet the child's appetite and heighten the intensity of need.[29]

Children said to have "hyperactivity" are described as "emotionally labile."[39] Accompanying their substantial array of inconsistent behaviors is a tendency toward capriciousness of mood or affect. Their behavior may vary from moment to moment, their personalities seeming to change with little provocation or justification. Wide mood swings are common and difficult to account for.[43]

COMMON CONCOMITANTS

Complicating the clinical scenarios is the recognition that these heterogeneous manifestations are accompanied by equally varied concomitant disabilities. Many (but by no means all) children with symptoms of hyperactivity also have learning disabilities.[18,45] These may range from problems with visual-spatial orientation, to difficulties with the processing of sequentially presented information, to specific language disabilities. Often the information-processing problem in itself is a disorganizing influence, impairing attention, precipitating impulsive behavior, and contributing to the child's poor self-esteem. Some youngsters said to be hyperactive also manifest significant delays in gross and/or fine motor function and visual motor integration.[9,31,45,46] Again, such associations are by no means invariable.

Social failure is another common concomitant. Many such children have difficulty forming, sustaining, and understanding peer relationships.[47,48] Their impulsivity may be threatening to other children. They may be imperceptive socially, unable to interpret or act on visual and verbal cues from others, and lack a social feedback response system. They may have difficulty predicting the social consequences of their acts. Ultimately they may experience increased social alienation, peer rejection, and stigmatization, all of which can intensify their anxiety, alter affect, and diminish self-esteem.[49]

There is some evidence that children with problems of attention and activity exhibit minor neurological signs (sometimes called "soft signs"), including associated movements, dysdiadochokinetic movements, and other indicators of neuromaturational delay.[50,51] It may well be that one subset of children with problems of attention and activity actually manifest a delay in the maturation of the CNS.[52]

It is not surprising that children who endure academic failure, adult disapproval, peer rejection, and loss of control are likely to acquire secondary emotional problems.[53] Depression, psychosomatic symptoms, and sociopathic behavior may ensue. These may be the end products of chronic frustration, of mismatching to adult expectancies, and of long-standing failure. Nor is it surprising that, out of desperation, some youngsters appropriate maladaptive strategies to deal with their failures and to save face. Aggressive behavior, class clowning, social withdrawal, or blatant defiance of adult expectations may be examples of such defensive maneuvers. Sometimes these symptoms may be inappropriately attributed to primary emotional disturbances.

PHYSIOLOGICAL CORRELATES

Most studies have used behavioral criteria to select subjects and document outcomes. Among these have been investigations of physiological and biochemical parameters in this group of children. Several investigators have concluded that some of these youngsters have aberrations in their CNS metabolism of biogenic amines.[54,55] Others have investigated various electrophysiological parameters, including EEG findings, evoked cortical potentials, and autonomic nervous system responses, in an attempt to define common pathophysiological mechanisms or to preselect those children who will respond to medication.[56]

ACKNOWLEDGING HETEROGENEITY

In view of the heterogeneity of this group of children, it is unlikely that there will emerge a unitary biochemical or physiological explanation for "hyperactivity." Nevertheless, further studies may allow us to define subgroups of these children with biochemical or physiological criteria. Meanwhile, given the multitude of constellations and severities of manifestations in this population, the process of sample selection for a research project is hazardous.[5] It is imperative that future investigation offer more detail in the description of the population studied, because the natural history and treatment of a child who has attention problems and a language disability may be quite different from those of a child whose dysfunction is accompanied by no information-processing problems whatsoever. Likewise, those youngsters whose major manifestation is impulsivity may have a different prognosis and pathophysiology from those whose problems exist mainly in the areas of selective attention and work output. Lumping all such youngsters together to describe a natural history is likely to result in a growing mass of nonreplicable research.[17]

Recently there has been considerable interest in the term *attention deficit disorder*. This too may turn out to be an overly inclusive categorization. We have suggested one approach toward the differentiation among children thought to have attention problems.[25,29] This is given in Table 2. Some children seem to have a *primary attention deficit*. They are thought, on

Table 2.—Attention Deficits and Their Differentiation
Primary attention deficit Constitutional neurological weakness of selective attention Variable clinical manifestations (see Figure) Present through most of child's life Pervasive in multiple settings
Secondary attention deficit Inattention as a response to one or more deficits in information processing (ie, learning disabilities) Outward symptoms similar to primary attention deficit May not be manifest until vulnerable areas of learning are challenged or Inattention as a result of emotional preoccupations (ie, chronic "drainage" of attention), losses, or psychosocial problems Outward symptoms similar to primary attention deficit
Situational inattention Inattention precipitated by "mismatching" of child with settings and/or expectations Likely to be present exclusively or primarily in specific places or circumstances
Mixed forms Combinations of other forms relative importance of components may evolve with age

a clinical basis, to have relatively "pure" problems with selective attention, a primary constitutional disorder in the CNS "circuits"; yet it must be emphasized that, even within this group, there is considerable symptomatic heterogeneity. For example, some such children may have predominant impulsivity, others sleep-arousal problems, whereas others primarily have a high level of distractibility.

Another subgroup have *secondary attention deficits*. These children are likely to manifest many of the same symptoms as those with primary attention deficits, but their inattention is secondary either to an information processing problem (such as a receptive language disability or a disorder of short-term memory) or, alternatively, to significant emotional preoccupations and anxieties. Children with information-processing problems may "tune out" and become inattentive, fidgety, and impulsive as a response to the futility of struggling to decode words or perceive symbols. Children with serious psychosocial problems may be "drained" of attentional strength because their thoughts are elsewhere.

Situational inattention is a less pervasive form of attention deficit, which is situation-specific in that it is likely to be the result of mismatchings between external expectations and a child's characteristics. An incorrect school or classroom placement may precipitate inattention, or a child whose home value system and cultural milieu differ significantly from those in the school may become inattentive and disorganized in the classroom.

Finally, one must acknowledge the existence of *mixed forms* of chronic attention deficit. Some children may have primary weaknesses of attention accompanied by learning disorders and anxiety. Some also will have situational inattention, as they are placed in classrooms that may not meet their needs. A basic differentiation, such as this, can be important in educational planning and in the design of studies of natural history as well as for intervention.

From a clinical standpoint, each child needs to be assessed as an individual person rather than as a representative of a syndrome.[57] His or her unique array of traits (Figure) will be the major determinant of therapy, of educational planning, and of the type of counseling and anticipatory guidance. The clinician must be sensitive to the fact that, although these children are likely to share some traits in common, there is marked heterogeneity and major differences among them with regard to service needs.

When one turns to the question of cause, there may be even more variation. It is likely that widely diverse causes exist, ranging from genetic determinants, to perinatal stresses, to acquired CNS insults, early environmental influences, and perhaps combinations of these.[5,39,58]

CONCLUSION

Although they are far from conclusive, studies of adult outcome reinforce the notion that there exists a highly vulnerable subset of our children, that early identification is likely to be crucial, and that we need to direct our clinical and research efforts toward enhancing their quality of life. It would seem, however, injudicious to presume homogeneity among these children. We are in fact *not* dealing with a well-circumscribed syndrome or functional disease entity. Hyperactivity is more than a symptom. It is also more than a symptom complex. The behaviors enumerated represent nonspecific symptoms, the outward indicators that not all is well at the interface between an environment and a possibly disordered CNS.[59] It may be that an attention deficit is to developmental dysfunction as fever is to infection. As a clinical phenomenon, it is unlikely ever to become etiologically and therapeutically specific. It should be conceptualized as a vital subject area for developmental pediatrics (and other disciplines) rather than a clearly definable syndrome. It is likely that "hyperactivity" is both a complex symptom and a complex symptom complex. We prefer not to use the term!

References

1. Weiss G, Hechtman L, Perlman T, et al: Hyperactives as young adults: A controlled prospective ten-year follow-up of 75 children. *Arch Gen Psychiatry* 36:657-681, 1979.
2. Laufer MW: Long-term management and some follow-up findings on the use of drugs with minimal cerebral syndromes. *J Learning Dis* 4:55-58, 1971.
3. Mendelson W, Johnson N, Stewart MA: Hyperactive children as teenagers: A follow-up study. *J Nerv Ment Dis* 153:273-279, 1971.
4. Huessy HR, Metoyer M, Townsend M: Eight- to ten-year follow-up of 84 children treated for behavior disorder in rural Vermont. *Acta Paedopsychiatr* 40:230-235, 1974.
5. Ross DM, Ross SA: *Hyperactivity: Research, Theory, and Action*. New York, John Wiley & Sons Inc, 1976.
6. Bugental DB, Whalen CK, Henker B: Causal attributions of hyperactive children and motivational assumptions of two behavior-change approaches: Evidence for an interactionist position. *Child Dev* 48:874-884, 1977.
7. Conners CK: A teacher rating scale for use in drug studies with children. *Am J Psychiatry* 126:884-888, 1969.
8. Coleman M: Serotonin concentration in whole blood of hyperactive children. *J Pediatr* 78:985-990, 1971.
9. Conners CK, Taylor E, Meo G, et al: Magnesium pemoline and dextroamphetamine: A controlled study in children with minimal brain dysfunction. *Psychopharmacologia* 26:321-336, 1972.
10. Greenberg LM, Deem MA, McMahon S:

Effects of dextroamphetamine, chlorpromazine, and hydroxyzine on behavior and performance in hyperactive children. *Am J Psychiatry* 129:532-539, 1972.

11. Greenhill L, Puig-Antich J, Sassin J, et al: Hormone and growth response in hyperkinetic children on stimulant medication. *Psychopharm Bull* 13:33-36, 1977.

12. Conners CK: Symptom patterns in hyperkinetic, neurotic, and normal children. *Child Dev* 41:667-682, 1970.

13. Harvey DHP, Marsh RN: The effects of decaffeinated coffee versus whole coffee on hyperactive children. *Develop Med Child Neurol* 20:81-86, 1976.

14. Rapoport JL, Quinn PO, Bradbard G, et al: Imipramine and methylphenidate treatments of hyperactive boys. *Arch Gen Psychiatry* 30:789-793, 1974.

15. Satterfield J, Cantwell D, Lesser L, et al: Physiological studies of the hyperkinetic child. *Am J Psychiatry* 128:1418-1424, 1972.

16. Stewart MA, Thach BT, Freidin MR: Accidental poisoning and the hyperactive child syndrome. *Dis Nerv Syst* 31:403-407, 1970.

17. Schain RJ, Reynard CL: Observations on effects of a central stimulant drug (methylphenidate) in children with hyperactive behavior. *Pediatrics* 55:709-716, 1975.

18. Stewart MA, Pitts FN, Craig AG, et al: The hyperactive child syndrome. *Am J Orthopsychiatry* 36:861-867, 1966.

19. Barkley RA: A review of stimulant drug research with hyperactive children. *J Child Psychol Psychiatry* 18:137-165, 1977.

20. Myers GJ, Pless IB: Where's the hyperactive child going? *Pediatrics* 57:1-3, 1976.

21. Shaffer D, Greenhill L: A critical note on the predictive validity of "The Hyperkinetic Syndrome." *J Child Psychol Psychiatry* 20:61-72, 1979.

22. Wolraich ML: Stimulant drug therapy in hyperactive children: Research and clinical implications. *Pediatrics* 60:512-518, 1977.

23. Ross AO: *Psychological Aspects of Learning Disabilities and Reading Disorders:* New York, McGraw-Hill Book Co, 1976.

24. Eisenberg L: The clinical use of stimulant drugs in children. *Pediatrics* 49:709-715, 1972.

25. Levine MD, Liden CB: Food for inefficient thought. *Pediatrics* 58:145-148, 1976.

26. Nichamin SJ: Recognizing minimal cerebral dysfunction in the infant and toddler. *Clinical Pediatr* 11:255-257, 1972.

27. Wender PH: *Minimal Brain Dysfunction in Children.* New York, John Wiley & Sons Inc, 1971.

28. Cantwell DP: Epidemiology, clinical picture, and classification of the hyperactive child syndrome, in Cantwell DP (ed): *The Hyperactive Child.* New York, Spectrum Publications Inc, 1975, pp 3-15.

29. Levine MD, Brooks R, Shonkoff J: *A Pediatric Approach to Learning Disorders.* New York, John Wiley & Sons Inc, 1980.

30. Forness S: Educational approaches with hyperactive children, in Cantwell DP (ed): *The Hyperactive Child.* New York, Spectrum Publications Inc, 1975, pp 59-72.

31. Keogh B: Hyperactivity and learning disorders: Review and speculation. *Except Child* 38:101-109, 1971.

32. Kinsbourne M, Caplan PJ: *Children's Learning and Attention Problems.* Boston, Little Brown & Co, 1979.

33. Sykes DH, Douglas VI, Greiss G, et al: Attention in hyperactive children and the effect of methylphenidate (Ritalin). *J Child Psychol Psychiatry* 12:129-139, 1971.

34. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III). Washington, DC, American Psychiatric Association, to be published.

35. Werry JS: Developmental hyperactivity. *Pediatr Clin North Am* 15:581-599, 1968.

36. Cohen NJ, Weiss G, Minde K: Cognitive styles in adolescents previously diagnosed as hyperactive. *J Child Psychol Psychiatry* 13:203-209, 1972.

37. Browning RM: Hyporesponsiveness as a behavioral correlate of brain damage in children. *Psychol Rep* 20:251-259, 1967.

38. Whalen CK, Henker B: Psychostimulants and children: A review and analysis. *Psychol Bull* 83:1113-1130, 1976.

39. O'Malley JE, Eisenberg L: The hyperkinetic syndrome. *Semin Psychiatry* 5:95-103, 1973.

40. Maccoby EE, Dowley EM, Hagen JW, et al: Activity level and intellectual functioning in normal preschool children. *Child Dev* 36:761-770, 1965.

41. Campbell SB, Douglas VI, Morgenstern G: Cognitive styles in hyperactive children and the effect of methylphenidate. *J Child Psychol Psychiatry* 12:55-67, 1977.

42. Sykes DH, Douglas VI, Morgenstern G: Sustained attention in hyperactive children. *J Child Psychol Psychiatry* 14:213-220, 1973.

43. Laufer M, Denhoff E: Hyperkinetic behavior syndrome in children. *J Pediatr* 50:463-474, 1957.

44. Satterfield JH: Neurophysiological studies with hyperactive children, in Cantwell DP (ed): *The Hyperactive Child.* New York, Spectrum Publications Inc, 1975, pp 67-82.

45. Conners CK: The syndrome of MBD: Psychological aspects. *Pediatr Clin North Am* 14:749-766, 1967.

46. Anderson WW: The hyperkinetic child: A neurological appraisal. *Neurology* 13:968-973, 1963.

47. Stewart MA, Olds SW: *Raising a Hyperactive Child.* New York, Harper & Row Publishers Inc, 1973.

48. Wender PH: *The Hyperactive Child: A Handbook for Parents.* New York, Crown Publishers Inc, 1973.

49. Zrull JP, McDermott JF, Poznanski E: Hyperkinetic syndrome: The role of depression. *Child Psychiatry Human Dev* 1:33-40, 1970.

50. Denckla MB, Rudel RG: Anomalies of motor development in hyperactive boys. *Ann Neurol* 3:231-233, 1978.

51. Werry J, Minde K, Guzman A, et al: Studies on the hyperactive child: VII. Neurological status compared with neurotic and normal children. *Am J Orthopsychiatry* 127:824-825, 1972.

52. Satterfield JH: EEG issues in children with minimal brain dysfunction. *Semin Psychiatry* 5:35-46, 1973.

53. Weiss G, Minde K, Werry J, et al: Studies on the hyperactive child: VIII. Five-year follow-up. *Arch Gen Psychiatry* 24:409-414, 1971.

54. Shaywitz SE, Cohen DJ, Shaywitz BA: The biochemical basis of minimal brain dysfunction. *J Pediatr* 92:179-187, 1978.

55. Ritvo ER: Biochemical research with hyperactive children, in Cantwell DP (ed): *The Hyperactive Child.* New York, Spectrum Publications Inc, 1975.

56. Satterfield JH: Neurophysiologic studies with hyperactive children, in Cantwell DP (ed): *The Hyperactive Child.* New York, Spectrum Publications Inc, 1975.

57. Weiss G, Hechtman L: The hyperactive child syndrome. *Science* 205:1348-1354, 1979.

58. Fish B: The "one child, one drug" myth of stimulants in hyperkinesis: Importance of diagnostic categories in evaluating treatment. *Arch Gen Psychiatry* 25:193-203, 1971.

59. Battle ES, Lacey B: A context for hyperactivity in children, over time. *Child Dev* 43:757-773, 1972.

Radiological Case of the Month

Lionel W. Young, MD; Contributed by I. Gershman, MD, Peter R. Simon, MD, MPH

A 17-year-old girl was evaluated at the Roger Williams General Hospital, Providence, RI, because of multiple injuries received during an assault. Roentgenograms of her pelvis and long bones showed no evidence of fractures or dislocations (Fig 1). However, an unusual pattern was noted in the bones.

She previously had been well, without complaints of limb or bone pain, joint swelling or stiffness. Her parents, both 40 years old, were unrelated by birth and came from mixed ethnic backgrounds. Pelvic roentgenograms of her father (Fig 2) and her 13-year-old brother (Fig 3) showed similar skeletal patterns, but her sister and mother were unaffected.

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Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Young).

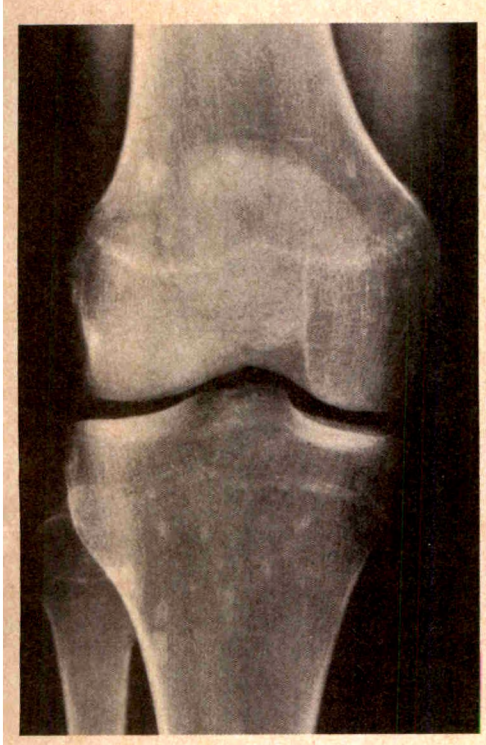

Figure 1.—Left

Figure 1.—Center

Figure 1.—Right

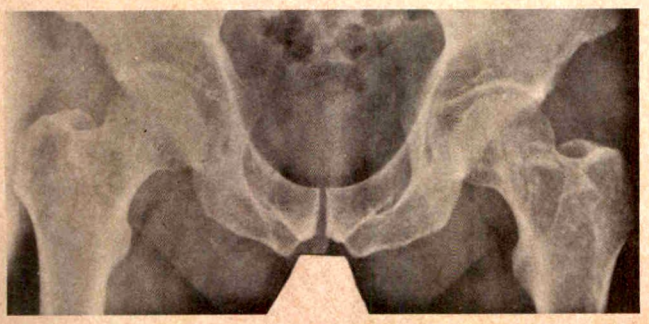

Figure 2.

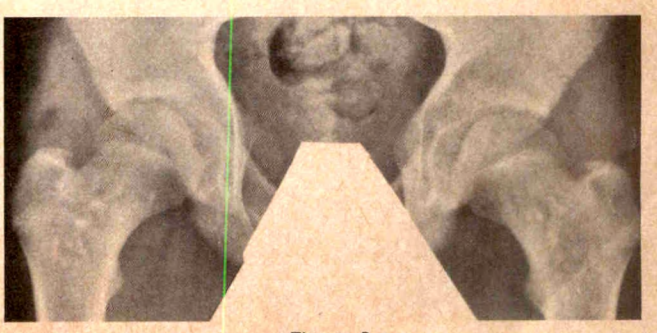

Figure 3.

Denouement and Discussion

Fig 1.—Patient's left knee, with both anteroposterior (left) and lateral (center) views. At right, patient's left elbow.

Fig 2.—Patient's father's hips.

Fig 3.—Patient's brother's hips.

Osteopoikilosis: Familial Documentation

Osteopoikilosis (spotted bones) is a rare, clinically harmless condition classified in the orthopedic and pathology literature[1] as an anomaly of bone. It has been reported about 150 times in series published in both the radiologic and orthopedic literature.[1,2]

The condition, although first reported in 1905 by Stieda,[3] was fully described clinically in 1914 by Albers-Schonberg[4] and Ledoux-Lebard et al,[5] and histopathologically by Schmorl[6] in 1931. Usually, the diagnosis of osteopoikilosis is a chance discovery on a roentgenographic examination for other reasons. Affected individuals show small foci of compact osseous tissue interspersed through the spongy bone. The spotted or mottled appearance on roentgenogram is produced by these discrete or clustered, round or slightly oval radiopacities.

This entity is uncommon. Jonasch,[7] in a series of 211,000 unselected roentgenograms, identified only 12 cases (six cases per 100,000). Reports tend to suggest that it occurs most often between the ages of 15 and 60 years of age although cases in newborns and even a 4-month-old fetus[8] have been discovered. No sex seems to be preponderant.

The etiology of the condition is unknown. However, autosomal dominant mendelian inheritance with variable expressivity has been established. In one family, the condition has been shown in four generations.[2]

A multitude of conditions have been reported as associated with osteopoikilosis.[9] Dermatofibrosis lenticularis disseminata and subcutaneous fibrous nodules are the two most commonly mentioned. Whether these and other conditions show an increased incidence in the presence of osteopoikilosis has not been documented. Osteopoikilosis is a benign condition, with little or no clinical importance, and should not be confused with more serious disorders of bone.[10]

References

1. Green AE Jr, Ellswood WH, Collins JR: Melorheostosis and osteopoikilosis. *Am J Roentgenol* 87:1096-1111, 1962.
2. Melnick JL: Osteopathia condensans disseminata (osteopoikilosis). *Am J Roentgenol* 82:229-238, 1959.
3. Stieda A: Uber umschriebene Knochenverdichtungen im bereich der substantia spongiosa im rontgenbilde. *Beitr Klin Chir* 45:700-703, 1905.
4. Albers-Schonberg HE: A rare unknown structural anomaly of the skeleton. *Fortschr geb Röntgenstrahlen* 23:174-175, 1915.
5. Ledoux-Lebard R, Chabaneix, Dessane: L'ostéopoécilie, forme nouvelle d'ostéite condensante generalisée sans symptomes cliniques. *J Radiol Électrol* 2:133-134, 1916.
6. Schmorl G: Anatomische Befunde bei einem falle von Osteopoikilie. *Fortschr geb Röntgenstrahlen* 44:1-8, 1931.
7. Jonasch E: 12 Falle von Osteopoikilie. *Fortschr geb Röntgenstrahlen* 82:344-353, 1955.
8. Martincić N: Case reports: Osteopoikilie (spotted bones). *Br J Radiol* 25:612-614, 1952.
9. Henson A: Familial osteopoikilosis. *Am J Surg* 45:566-573, 1939.
10. Wachtel G: Über einen Fall von Osteopathia condensans disseminata. *Fortschr Röntgenstr* 21:624-625, 1919.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Clinical Memoranda

Pseudodiverticulum of the Esophagus in the Newborn Infant

Atresia of the esophagus, with or without tracheoesophageal fistula, is the most common congenital malformation of the upper gastrointestinal (GI) tract. Duplication of the esophagus and diverticulum (outpouching of all layers of the esophagus) are among the rare but still important congenital esophageal lesions. Lack of continuity of the esophageal wall could be congenital, disease related, or the end result of a diagnostic or therapeutic maneuver.

See p 367.

A pseudodiverticulum is a traumatic perforation of the esophagus that affects only the mucosa and submucosa but spares the muscularis.[1] The lack of familiarity with its clinical and radiologic signs may result in unnecessary diagnostic delays or therapeutic misadventures. Fourteen cases of esophageal pseudodiverticulum have previously been reported in the literature. To our knowledge, this report is of the smallest premature infant affected with this condition, who was treated conservatively and experienced prolonged spontaneous closure.

Report of a Case.—A female infant was born at 28 weeks of gestation to a 17-year-old girl. Apgar scores were 3 at one minute and 8 at five minutes. Oropharyngeal suctioning with a polyvinyl de Lee catheter and endotracheal intubation were necessary before the resuscitation was completed. The birth weight was 960 g, appropriate for age at about 28 weeks' gestation.

One hour after admission, the patient had respiratory failure requiring endotracheal intubation and artificial ventilation on a pressure-controlled respirator. At 4 hours of age, large amounts of mucous material were suctioned with a de Lee catheter from the oropharynx. One hour later, several attempts to place an orogastric tube failed. A chest and abdominal film showed the position of the orogastric tube to be at the upper third of the esophagus, the absence of abdominal air, and a reticulogranular appearance. The infant was then placed on a regimen of nothing per mouth (NPO), and further diagnostic studies were delayed until the hyaline membrane disease (HMD) improved. The course of HMD peaked at 48 hours of life, with a right pneumothorax that was corrected by a polyvinyl hydrochloride thoracotomy tube insertion and continuous suction.

At 6 days of life, the patient was extubated, but owing to the recurrence of severe apneic spells, she had to be reintubated four hours later. Two days later, an orogastric tube was passed into the stomach without difficulty. This maneuver ruled out the possibility of a blind proximal esophageal pouch. Gavage feedings were started and promptly discontinued after they were found to be associated with cyanosis and respiratory distress. To rule out an H-type fistula, an intragastric oxygen test was performed,[2] which was negative. An esophagram was performed under fluoroscopy, identifying a pseudodiverticulum arising from the posterior pharyngeal wall at the C-5 level and extending inferiorly to the T-2 level. The same day, the infant was successfully extubated and the subsequent course was complicated only by one episode of atelectasis of the right lung, which was corrected by deep suctioning of the bronchial tree.

The patient received total parenteral nutrition for the first 18 days of life and was then given polytube feedings of lactose-free, medium triglycerides formula (Portagen). The indwelling orogastric catheters were replaced every third day without difficulties, and intermittent gavage feedings were restarted at 30 days of life and were continued for another month before nipple feedings.

The hospital course was transiently complicated by hyperbilirubinemia, ketonuria, and edema. At 67 days of age, an esophagram still indicated the presence of a pseudodiverticulum. One week later, the infant was discharged while feeding by nipple without difficulties.

Two weeks after discharge, she was admitted to Columbus (Ohio) Children's Hospital for evaluation of apneic spells. These episodes were considered to be seizure equivalents, and the patient was discharged on a regimen of elixir of phenobarbital sodium (5 mg/kg/day).

At 4 months of age, she had a viral laryngotracheobronchitis severe enough to require hospitalization. During this admission, a follow-up esophagram was performed, and complete disappearance of the pseudodiverticulum was documented. When examined at 8 months of age, the infant seemed to be growing and developing normally and to be able to eat solid food without difficulty.

Comment.—One of every two very small premature infants ($\leq$ 1,000 g) requires endotracheal intubation in the delivery room.[3] Oropharyngeal suctioning,[4-7] endotracheal intubation,[7,8] and nasogastric tube passage[9] have all been associated with pseudodiverticulum formation; and all these procedures were performed on our patient prior to the initial clinical signs. The most characteristic sign of a pseudodiverticulum is the failure to pass a nasogastric tube in the absence of esophageal atresia. This is thought to be due more to cricopharyngeal spasm than to penetration into the newly formed tract. Passage of an orogastric tube without difficulty, even when the lesion was still open, reinforces the concept that cricopharyngeal spasm may have been the main reason for the obstruction early in the course. Increased salivation, cyanosis, and dyspnea during feedings have also been associated with these rare lesions of the esophagus.[4-9]

Clinical Signs	No. of Cases
Increased salivation mucus drooling	9/15
Cyanosis and/or respiratory distress syndrome	9/15
Feeding difficulties, vomiting, choking	8/15
Inability to pass orogastric or nasogastric tube	7/15

At the time when an H-type esophageal fistula was considered, an intragastric oxygen test[2] was performed. This new technique is promising, but its accuracy should be evaluated with a larger patient series.

An esophagram is the diagnostic procedure of choice for visualization of the pseudodiverticulum. Roentgenographic signs of pseudodiverticulum have been observed by Ducharme et al and are based on location, configuration, and size of the lesion.[4] Adjunctive procedures are laryngoscopy and esophagoscopy.[4-7]

If one would wait until the cricopharyngeal spasm is over, it might be possible to pass an orogastric tube, ruling out esophageal atresia. In our case, orogastric passage was successfully done at the eighth day of life.

Although 14 cases of pseudodiverticulum have been reported to date,[1,4-6,8,9] this condition remains extremely rare. Ekloff et al[6] briefly mentioned six unreported cases, and we know of at least another one in our community. Considering the frequency of aggressive instrumentation of the upper airway and GI tract, we suspect this entity may occur more often than hitherto reported. Of the reported cases, information about gestational age was available in only nine instances. Four of these nine newborns were known to be premature. Seven patients underwent exploratory thoracotomy and resection, and ligation of the pseudodiverticulum was performed on four of them.

Ekloff et al[6] summarized their expe-

rience with three cases by strongly advocating a nonsurgical approach, close supervision, and polytube feedings. Astley and Roberts,[9] Ducharme et al,[4] and Edison and Holinger[5] endorsed the conservative approach of Ekloff et al. In the report by Girdany et al,[1] two patients were operated on and one died; and in the report by Armstrong et al,[8] the only patient on whom surgery was performed survived.

Since nonsurgical treatment has been successful in eight cases and spontaneous closure has been reported in 11 out of the 15 cases, it is our opinion that the treatment of pseudodiverticulum of the esophagus should be a conservative one. Spontaneous closure has been reported to occur between 3 to 124 days of life. In nine of 11 cases, this was documented before the 16th day of life, and it is likely that it may have occurred earlier. It would seem advisable to keep the patient on a regimen of NPO for at least two weeks while being supported by partial or total parenteral nutrition via a peripheral vein.[10] At that time, another esophagram should be performed, and if the pseudodiverticulum is by then closed, nipple feeding in the full-term infant and gavage feeding in the premature infant should be started. We do not advocate the use of gastrostomy as a feeding technique in this condition since it has been associated with increased mortality in the premature infant.[11] Furthermore, the natural history of this condition, the possibility of spontaneous early closure of the pseudodiverticulum, and the availability of total or partial parenteral nutrition support the conservative approach.

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1. Girdany BR, Sieber WK, Osman MZ: Traumatic pseudodiverticulums of the pharynx in newborn infants. *N Engl J Med* 280:237-240, 1969.

2. Korones SB, Evans LJ: Measurement of intragastric oxygen concentration for the diagnosis of H-type tracheoesophageal fistula. *Pediatrics* 60:450-452, 1977.

3. O'Brien JR, Usher RH, Maughan GB: Causes of birth asphyxia and trauma. *Can Med Assoc J* 94:1077-1085, 1966.

4. Ducharme JC, Bertrand R, Debie J: Perforation of the pharynx in the newborn: A condition mimicking esophageal atresia. *Can Med Assoc J* 104:785-787, 1971.

5. Edison B, Holinger PH: Traumatic pharyngeal pseudodiverticulum in the newborn infant. *J Pediatr* 82:483-485, 1973.

6. Ekloff O, Lohr C, Okmian L: Submucosal perforation of the esophagus in the neonate. *Acta Radiol* 8:187-192, 1969.

7. Lynch FP, Coran AG, Cohen SR, et al: Traumatic esophageal pseudodiverticula in the newborn. *J Pediatr Surg* 9:675-680, 1974.

8. Armstrong RG, Lindberg EF, Stanford W, et al: Traumatic pseudodiverticula of the esophagus in the newborn infant. *Surgery* 67:844-846, 1970.

9. Astley R, Roberts KD: Intubation perforation of the esophagus in the newborn baby. *Br J Rad* 43:219-222, 1970.

10. Heird WC, Anderson TL: Nutritional requirements and methods of feeding low birth weight infants. *Curr Probl Pediatr* 26-34, 1977.

11. Vengusamy S, Pildes RS, Raffensperger JF, et al: A controlled study of feeding gastrostomy in low birth weight infants. *Pediatrics* 43:815-820, 1969.

Successful Treatment of Rupture of Normal Spleen in Newborn

Diagnosis and successful repair of the ruptured spleen or liver in the newborn is rare. More autopsy diagnoses are reported[1-3] of this complication of delivery than diagnoses of surviving cases.[3-5] A case is reported where the diagnosis of a ruptured normal spleen was established and splenectomy was performed within the first 24 hours of life. The usefulness of the available diagnostic clinical and roentgenographic signs is discussed.

Report of a Case.—A 3.975-kg male infant was born after an uncomplicated 40-week gestation to a 17-year-old woman. Pertinent status of the mother was as follows: gravida 3, para 2, negative VDRL, and a blood type of group B, Rh positive. Labor was 2½ hours' duration. A pudendal block was used. Rupture of the membranes occurred 30 minutes before delivery; the baby was a vertex presentation. The one-minute Apgar score was 9. Maternal blood loss was estimated to be 300 mL. Cord blood hemoglobin level was 13.5 g/dL and the hematocrit level was 41.5%. The baby had group B, Rh positive blood with negative Coombs' test. Physical examination within 12 hours after birth showed a normal male newborn without signs of traumatic delivery. Routine nursery care was begun.

At 20 hours of age, after returning from feeding by the mother, the neonate became pale and tachypneic, and abdominal distention developed. Systolic blood pressure was undetectable. Rectal examination and return from nasogastric tube showed no blood in the rectum or stomach, respectively. He received a transfusion of 30 mL of blood after a blood sample was obtained. Laboratory studies disclosed the following values: hemoglobin, 6.4 g/dL; hematocrit, 17.2%; and WBCs, platelets, reticulocytes, total bilirubin, and hemostasis were normal. An abdominal roentgenogram failed to visualize the stomach; no masses or calcifications were noted. Roentgenographic examination of the stomach showed anterior and medial displacement without extravasation of the opaque material. Paracentesis showed blood in the abdomen that did not clot. Posttransfusion hemoglobin and hematocrit levels were 7.1 mg/dL and 21.5%, respectively. The baby was given another transfusion of 50 mL of fresh whole blood.

At surgery, approximately 150 mL of blood and clots were found in the abdominal cavity. A large retroperitoneal nonpulsatile hematoma was found over the left kidney and extended inferiorly to the level of the aortic bifurcation. The posterior surface of the spleen showed a capsular tear at the splenorenal ligament. There were no thoracic or diaphragmatic contusions and no intra-abdominal or retroperitoneal abnormalities.

A splenectomy was performed. Salvage of spleen was not performed due to the gravity of patient's condition. The postoperative course was uneventful.

The spleen weighed 7 g and measured 4.5 × 3.0 × 1.5 cm. The capsular surface was normal with the exception of the capsular and parenchymal tear at the posterior hilar area. Results of the histopathologic examination were normal.

Comment.—The pathogenesis of the rupture of the spleen during or after an uneventful delivery is an enigma.[6] Gruenwald[1] believed that an important mechanism is an increased intrathoracic pressure that forces the liver and spleen out of the diaphragmatic hollow, causing severe tension in their supporting ligaments.

Our patient was a full-term male without primary disease and the delivery was neither precipitous nor difficult. The spleen was normal in size and structure. A splenic tear at the site of implantation of splenorenal ligament was found. Therefore, it seems that an unusual pressure on our patient's thorax might have caused rupture of a normal spleen.

Splenic rupture is a surgical emergency and the diagnosis becomes more difficult when one deals with nontraumatic delivery and an otherwise normal newborn. One must keep in mind the following two important observations: first, normal labor and delivery do not exclude the diagnosis of intra-abdominal trauma and second, splenic rupture occurs in two

stages—formation of a subcapsular hematoma, followed by urgent symptoms that occur only when the capsule eventually gives way. This is why the classical triad of unexplained blood loss, abdominal distention, and roentgenographic evidence of intraperitoneal fluid[4] is not always present.[5]

Several roentgenographic findings are consistent with splenic trauma: total body opacification,[7] free abdominal fluid, and "floating" gas-filled loops in a plain film, displacement of the stomach.[8] However, no single group of roentgenographic findings is consistently associated with splenic trauma.[9]

In our patient, the diagnosis of splenic rupture was established and operation was performed within the first 24 hours of life after an abdominal paracentesis showed hemoperitoneum. Although abdominal paracentesis led to more prompt diagnosis and operative intervention during the second stage of splenic rupture, we believe that all of the available diagnostic tools, including splenic scintiscan,[10] should be used to establish the diagnosis at an earlier stage when splenic salvage[11,12] may be performed. The latter is important, particularly in the very young infant to avoid overwhelming infection after splenectomy.[13]

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1. Gruenwald P: Rupture of liver and spleen in the newborn infant. *J Pediatr* 33:195-201, 1948.

2. Potter EL: Fetal and neonatal deaths: A statistical analysis of 2,000 autopsies. *JAMA* 115:996-1001, 1940.

3. Sieber WK, Girdany BR: Rupture of the spleen in newborn infants: Recovery after splenectomy. *N Engl J Med* 259:1074-1076, 1958.

4. Delta BG, Eisenstein EM, Rothenberg AM: Rupture of a normal spleen in the newborn: Report of a survival and review of the literature. *Clin Pediatr* 7:373-376, 1968.

5. Leape LL, Bordy MD: Neonatal rupture of the spleen: Report of a case successfully treated after spontaneous cessation of hemorrhage. *Pediatrics* 47:101-104, 1971.

6. Schwartz O, Cohn BD: Rupture of the normal spleen in the newborn, with survival. *Surgery* 59:1124-1127, 1966.

7. O'Connor JF, Neuhauser EBD: Total body opacification in conventional and high dose intravenous urography in infancy. *Am J Roentgen* 90:63-71, 1963.

8. Griscom NT: The roentgenology of neonatal abdominal masses. *Am J Roentgen* 93:447-463, 1965.

9. Schwartz SS, Boley SJ, McKinnon WMP: The roentgen findings in traumatic rupture of the spleen in children. *Am J Roentgen* 82:505-509, 1959.

10. Fischer KC, Rossello P, Eraklis A, et al: Non-operative treatment of children with splenic rupture: Extended follow-up with scintigraphic assessment of healing, abstracted. *J Nucl Med* 18:596-597, 1977.

11. Mishalany H: Repair of the ruptured spleen. *J Pediatr Surg* 9:175-178, 1974.

12. Matsuyama S, Suzuki N, Nagamachi Y: Rupture of the spleen in the newborn: Treatment without splenectomy. *J Pediatr Surg* 11:115-116, 1975.

13. Balfanz JR, Nesbit ME, Jarvis C, et al: Overwhelming sepsis following splenectomy for trauma. *J Pediatr* 88:458-460, 1976.

Neonatal Death Associated With Acute Transplacental Ethanol Intoxication

Alcohol is known to produce fetal teratogenicity,[1] neonatal withdrawal,[2] and acute transplacental intoxication.[3] We report a case of death in a neonate attributed to transplacental alcohol, used in an attempt to prevent premature parturition.

Report of a Case.—The mother, a 20-year-old primigravida in her 32nd week of an uncomplicated pregnancy, was prescribed strict bed rest and oral vodka, 30 mL thrice daily, to retard early onset of labor. Two days later, with continued contractions, the amount was increased and consumed in the volume of 30 mL/hr. Twelve hours thereafter, she was hospitalized with regular contractions and a slightly bloody vaginal discharge.

A single intravenous (IV) dose of 10 mg of morphine sulfate and a continuous IV drip of 10% ethanol were administered. During the next four hours, she became progressively intoxicated, unresponsive, areflexic, and unconscious, necessitating discontinuation of the ethanol drip; a total of 160 g of ethanol had been administered.

Two hours later, an amniotomy was performed followed by immediate vertex delivery of a severely depressed 1,420-g female infant. Apgar scores were 2 at one minute and 3 at five minutes. Normal fetal heart rates by auscultation were recorded up to half an hour before delivery; none were monitored thereafter. Resuscitation required endotracheal intubation, bag-to-tube ventilation with 100% oxygen, and IV infusions of sodium bicarbonate and epinephrine hydrochloride. Despite these efforts, the infant remained cyanotic, flaccid, unresponsive, and intermittently bradycardiac, and she had no spontaneous respiratory effort. Her temperature decreased to 34 °C. Umbilical venous blood gases at half an hour of life showed a Po_2 of 26 mm Hg, a Pco_2 of 74 mm Hg, and a pH of 7.05. Vigorous supportive measures were continued.

The infant was transported from the community hospital to the newborn intensive care center at the University of Utah, Salt Lake City, arriving at 5 hours of life. On our initial examination, in addition to the persistence of the previously described morbid findings, we found fixed dilated pupils, hypotension, and poor peripheral perfusion. The umbilical arterial blood pressure was 28 mm Hg. Hypothermia had been corrected. Laboratory studies revealed a nearly pure metabolic acidosis, a pH of 7.15, a Pco_2 of 43 mm Hg, and a base deficit of 15 mEq/L. This degree of metabolic acidosis persisted, despite base therapy and blood volume correction. The central hematocrit was 58%. Oxygenation remained marginal at best despite 100% inspired oxygen and artificial ventilation. A chest roentgenogram showed diffuse patchy infiltrates. Blood and CSF cultures indicated no growth of organisms.

The infant died at 56 hours of age, having shown persistent hypoxia, metabolic acidosis, and progressive bradycardia. Permission for an autopsy was denied. The mother resumed full consciousness during a 24-hour period after delivery.

Comment.—The Table lists serial blood alcohol levels as obtained for this mother and her infant. Therapeutic levels for prevention of premature parturition range from 90 to 160 mg/dL, intoxication at 200 to 300 mg/dL, coma at 350 to 500 mg/dL, and deaths have occurred at 450 to 500 mg/dL. Toxic levels have not been published for neonates. This mother's course correlated well with her alcohol intake and recorded blood levels.

Ethanol crosses the placental barrier freely; cord blood levels are about 20% lower than simultaneous maternal levels.[4] Elimination of alcohol is delayed in neonates, at a rate only about half as fast as their mothers[5]; in our patient, the rate of decrease in blood alcohol concentration was 15 mg/dL/hr while the mother's rate was 27 mg/dL/hr. Alcohol dehydrogenase activity is known to be low in human fetal liver, reaching only 20% of adult activity by term, a reasonable explanation for delayed metabolism of alcohol in newborns.[6] One might have expected that, as our infant's serum level decreased, there would have been noticeable clinical improvement, which was not observed. We suggest severe and prolonged ethanol toxic effects produced irreversible damage either directly from alcohol or indirectly through induced severe metabolic acidosis, with subsequent hypoxia and shock in this neonate. Transplacental ethanol has been shown to produce severe metabolic acidosis in fetal sheep.[7] We speculate that alcohol was

Blood Ethanol Levels for Infant and Mother

No. of Hours After Delivery	Serum Ethanol, mg/dL	
	Infant	Mother
5	715	...
6	...	473
9	588	...
10	...	383
14	477	277
22	381	54
40	235	...
52	97	...

responsible for this infant's moribund state. We cannot know to what extent prematurity, a history of vaginal bleeding of unresolved etiology, or maternal morphine infusion added to the effects of alcohol or contributed independently to this infant's death. Further case reporting and animal experimentation is needed to delineate the toxicity of alcohol for the fetus and neonate.

Acute neonatal ethanol intoxication has been reported when mothers consumed excessive amounts of alcohol[3] and when premature infants received IV fluids containing alcohol[8]; to our knowledge, neonatal death from alcohol has not been reported previously. This case has important implications for both the obstetrician and the pediatrician.

Published support for the oral use of alcohol in delaying parturition is limited.[9] Controversy even exists concerning the efficacy of intravenously administered alcohol.[10,11] As the present case illustrates, orally administered alcohol may act cumulatively with IV alcohol. Both a threatened premature labor and the use of alcohol to prevent it represent complex situations; hence, it seems appropriate to suggest that such patients should be managed in the hospital.

Treatment of severe fetal-neonatal ethanol intoxication should include prompt and vigorous resuscitation, with special attention to correction of metabolic acidosis. Care should be provided in a newborn intensive care unit. As far as we know, there have been no reported experiences of two additional logical modes of treatment of a severe neonatal ethanol toxic condition, namely, peritoneal dialysis and/or exchange transfusion. In view of ethanol's small molecular weight, high solubility, and primary distribution in the fluid phase of the body, peritoneal dialysis[12] or exchange transfusion may have a place in the treatment. Peritoneal dialysis has been used with success to reduce serum ethanol levels in an older child.[13] Both deserve more consideration.

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1. Hanson JW, Jones KL, Smith DW: Fetal alcohol syndrome: Experience with 41 patients. *JAMA* 235:1458-1460, 1976.
2. Pierog S, Chandavasu O, Wexler I: Withdrawal symptoms in infants with fetal alcohol syndrome. *J Pediatr* 90:630-633, 1977.
3. Cook LN, Shott RJ, Andrews BF: Acute transplacental ethanol intoxication. *Am J Dis Child* 129:1075-1076, 1975.
4. Ditts PV: Placental transfer of ethanol. *Am J Obstet Gynecol* 107:1195-1198, 1970.
5. Idanpaan-Heikkila J, Jouppila P, Akerblom HK, et al: Elimination and metabolic effects of ethanol in mother, fetus, and newborn infant. *Am J Obstet Gynecol* 112:387-393, 1972.
6. Pikkarainen P, Raiha NCR: Development of alcohol dehydrogenase activity in the human liver. *Pediatr Res* 1:165-168, 1967.
7. Mann LI, Bhakthavathsalan A, Liw M, et al: Placental transport of alcohol and its effect on maternal and fetal acid base balance. *Am J Obstet Gynecol* 122:837-847, 1975.
8. Peden VH, Sammon TJ, Downey DA: Intravenously induced infantile intoxication with ethanol. *J Pediatr* 83:490-493, 1973.
9. Luukkainen T, Vaisto L, Jarviene PA: The effect of oral intake of ethyl alcohol on the activity of the pregnant human uterus. *Acta Obstet Gynecol Scand* 46:486-493, 1967.
10. Zlatnik FJ, Fuchs F: A controlled study of ethanol in threatened premature labor. *Am J Obstet Gynecol* 112:610-612, 1972.
11. Graff G: Failure to prevent premature labor with alcohol. *Am J Obstet Gynecol* 110:878-880, 1971.
12. Marc-Aurele J, Achreiner GE: The dialysis of ethanol and methanol: A proposed method for the treatment of massive intoxication by ethyl or methyl alcohol. *J Clin Invest* 39:802-807, 1960.
13. Dickerman J, Bishop W, Marks J: Acute ethanol intoxication in a child. *Pediatrics* 42:837-840, 1968.

Intracranial Dermoid Cyst: Diagnosis by Computerized Tomography

Dermoid and epidermoid cysts are closely related benign, cystic tumors that occur throughout the CNS. Their slow growth may result in a long history of obscure symptoms, and they may attain large size with permanent neurologic impairment before the correct diagnosis is established. The angiographic appearance does not differ from other avascular masses. Computerized tomography (CT) can suggest a correct diagnosis.

Gawler et al[1] first described low absorption values in an intracranial, fat-containing dermoid cyst, as well as low absorption values in fat-containing craniopharyngiomas and teratomas. Other authors have reported both low and high absorption values in epidermoid cysts, apparently related to the nature of the contents.[2]

Report of a Case.—A 12-year-old girl's symptoms began approximately three years prior to this admission. At that time, she was noted to have a mild exophthalmus with no clinical evidence of hyperthyroidism; thyroid function studies showed no abnormalities. She was subsequently noted to have a rotational nystagmus, and conventional skull roentgenograms demonstrated a large calcific density in the region of the posterior fossa. The patient was seen by a neurosurgeon. Surgery was not advised because of the patient's satisfactory clinical course.

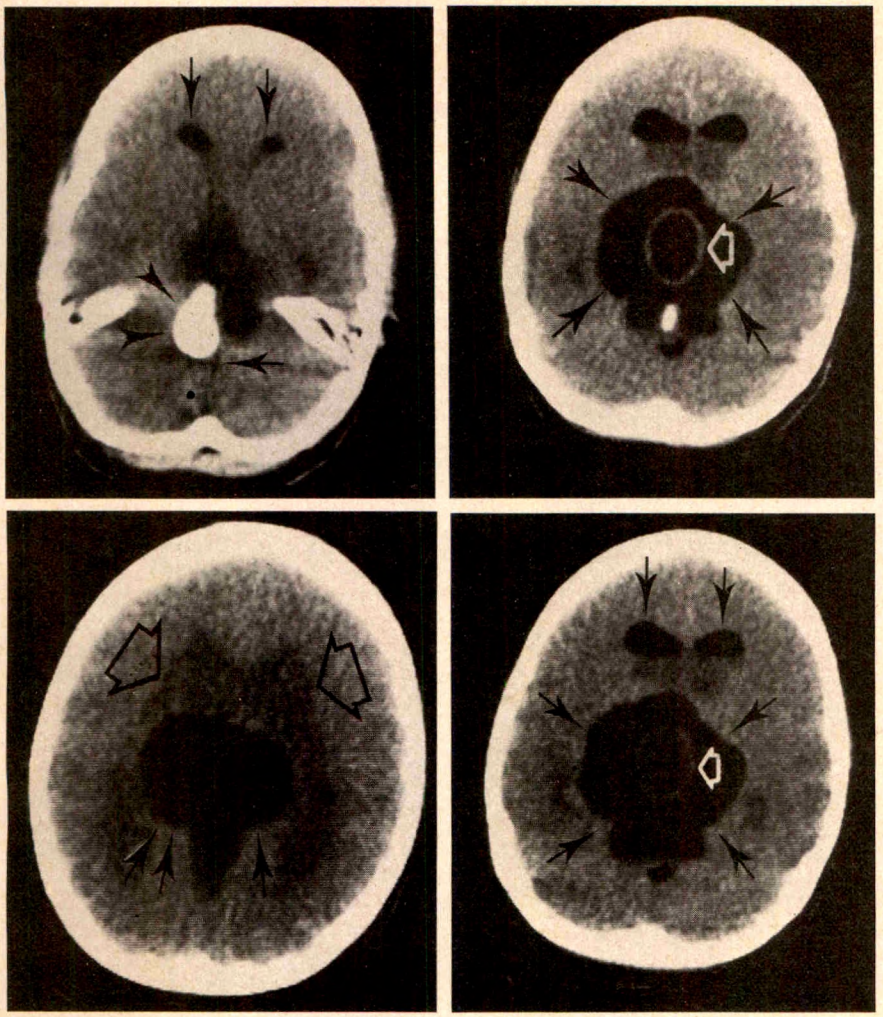
At age 12 years, the patient suddenly had severe bifrontal headaches, mild meningeal signs, and bilateral papilledema.

Cranial CT (Figure) showed a large, well-circumscribed cystic tumor of fat density. The tumor seemed to arise in the posterior fossa and to extend through the incisura dorsally, to the left of the falx cerebri, and inferiorly, to the lower margin of the fourth ventricle. There was severe ventricular dilation consistent with obstructive hydrocephalus. Free fat was noted in the lateral and third ventricles. The tumor contained a large calcific density. The free fat in the ventricles (low absorptive values) was indicative of intraventricular cyst rupture, a not uncommon complication of this lesion.

The patient underwent decompressive surgery, and a shunt procedure was performed, with notable clinical improvement. Definitive surgery was attempted three weeks later, but because of the large size, the tumor was not completely accessible and, therefore, was only partially excised. The patient had a difficult postoperative course, and on the sixth postoperative day, she became comatose and died. The operating surgeon believed that the tumor arose in the region of the pineal gland.

Histological studies indicated a cystic structure with a lining of stratified squamous epithelium. The cyst contained large quantities of keratin and hair. Dermal appendages, fat, and abnormally thick vessels were encountered in the walls of the cyst, along with foci of gliotic white matter. The opinion of the pathologist was that this represented a dermoid cyst arising posteriorly to the third ventricle.

Comment.—Pathologically, dermoid and epidermoid cysts of the CNS are cystic structures of variable size, sur-



Representative plain (top left and right and bottom left) and postcontrast injection (bottom right) scans. Top left, A "tooth"-shaped density (arrow heads) is present just above fourth ventricle (horizontal arrow) at level of pineal cistern. Fat (low absorptive values) fluid levels are present in frontal horns (vertical arrows). Top right, Image is at level of third ventricle and frontal horns. Fat-containing mass (diagonal arrows) has extended superiorly through tentorial incisura to collapse third ventricle, which is not visualized. Central loculation (open arrow), within cystic mass, is present. Fat fluid levels (vertical arrows) are present in frontal horns. Bottom left, Image is at level of lateral ventricles (open arrows), which are massively dilated due to obstruction at foramen of Monro. Mass (solid arrows) has extended between two lateral ventricles. Bottom right, Postintravenous contrast infusion computerized tomographic image at same level as image at top right. Periphery of mass (solid arrows) and central loculation (open arrow) is better visualized (enhanced) by contrast infusion.

rounded by a capsule of dense, fibrous connective tissue and lined by stratified squamous epithelium. Epidermoid cysts are lined solely by squamous epithelium. The lining of a dermoid cyst may also include skin appendages such as hair follicles, sweat, and sebaceous glands. Cyst contents may differ, with the dermoid cyst containing hair and large quantities of fat and with the epidermoid cyst containing only keratin, cellular debris, and cholesterol crystals.

The origin of these lesions is obscure. Most authors suspect a developmental process resulting from the inclusion of a segment of cutaneous ectoderm with neural ectoderm at the time the neural groove closes and separates, about the fourth week of gestation.[3] Trauma has been implicated in some of these tumors. A third possibility is that these lesions represent benign cystic teratomas that differentiate and develop from primitive totipotential embryonic rests, similar to dermoid cysts of the ovary.

The incidence of these lesions in the CNS has been estimated to 0.4% of all tumors, the epidermoid variety being more common than the dermoid. Epidermoids are also known as "pearly" tumors or cholesteotomas although they are not related to the cholesteotomas found in the middle ear in chronic mastoiditis. Dermoid cysts generally occur prior to age 20 years. Epidermoids tend to occur in older patients, with the peak incidence at about age 35 years.

These lesions tend to occur in the midline, usually in the juxtasellar or pineal regions or between the cerebellar hemispheres. Epidermoid cysts have been reported in the cerebellopontine angles and the ventricular system, especially the fourth ventricle.

Computerized tomography can be helpful as the fat within the cyst produces low absorptive values. Occasionally, epidermoid cysts will have high absorptive values, thought to be secondary to the high keratin content. When this is the case, the cysts cannot be differentiated from other solid tumor mass. Computerized tomography will demonstrate, as do conventional roentgenograms, the presence of teeth, bone, etc, as well as locating their position within the cyst.

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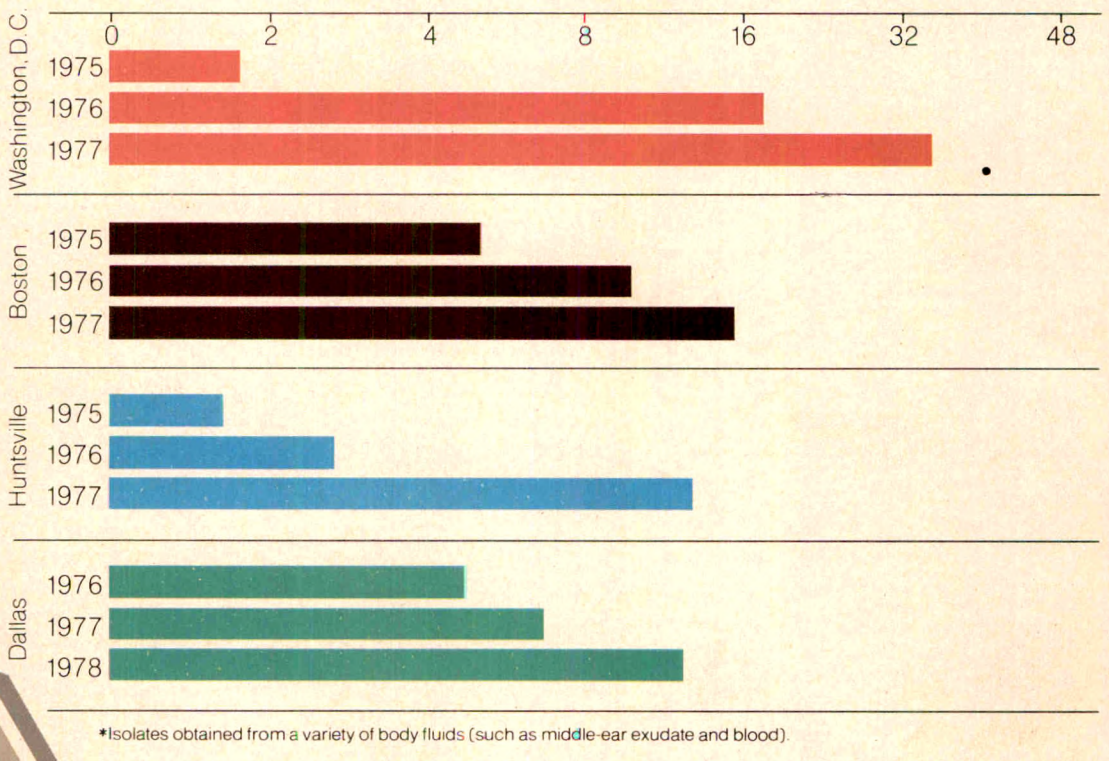
1. Gawler J, Bouley GH, Bull JWD, et al: Computer assisted tomography (EMI scanner): Its place in investigation of suspected intracranial tumors. *Lancet* 2:419-423, 1974.

2. Brain IF, Naidich TP, Leeds NE, et al: Dense intracranial epidermoid tumors. *Radiology* 122:717-719, 1977.

3. Fleming JFR, Botterell EH: Cranial dermoid and epidermoid tumors. *Surg Gynecol Obstet* 109:403-411, 1959.

Increasing resistance o



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor®(cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PE CILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCL ING ANAPHYLAXIS AFTER PARENTERAL USE)

Antibiotics, including Ceclor® (cefaclor, Lilly), should administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

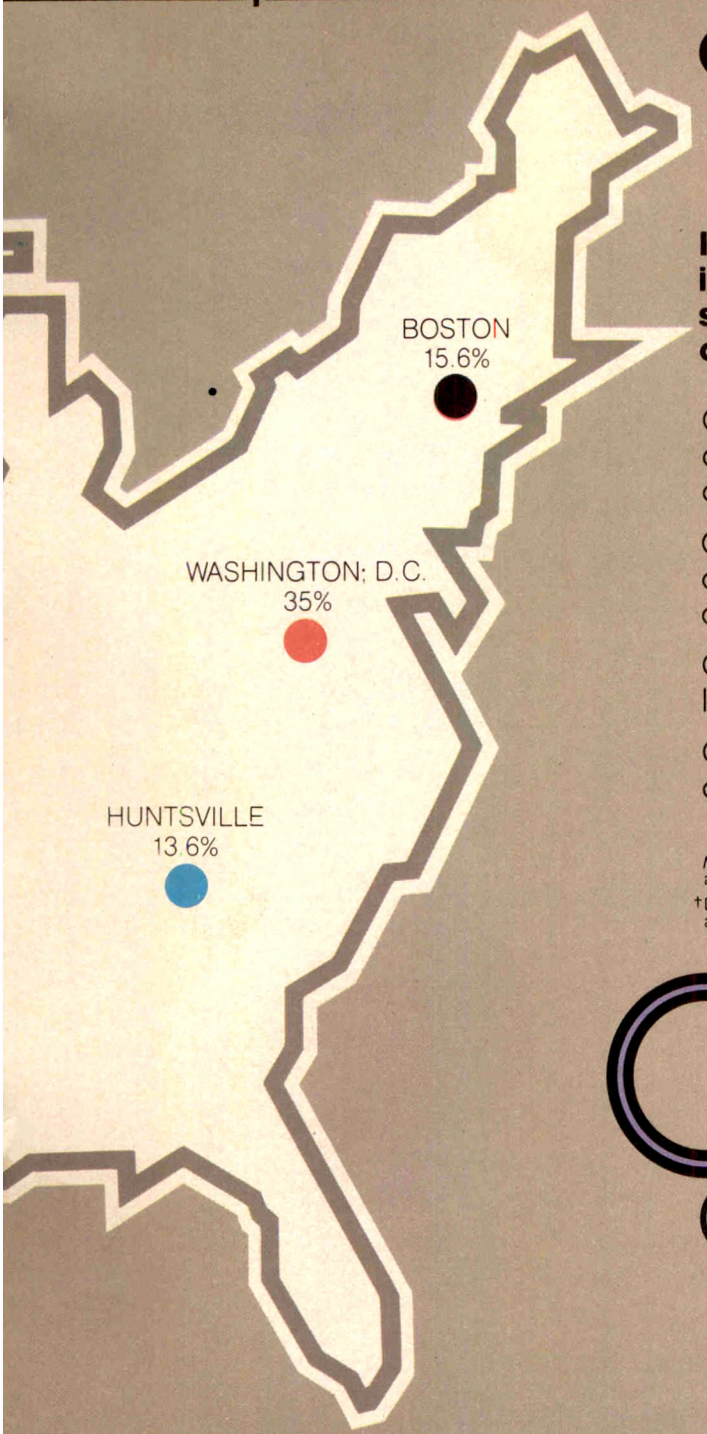
Precautions: If an allergic reaction to cefaclor occurs, th drug should be discontinued, and, if necessary, the pat should be treated with appropriate agents, e.g., presso amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrow of nonsusceptible organisms. Careful observation of th patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported duri treatment with the cephalosporin antibiotics. In hemato logic studies or in transfusion cross-matching procedu when antiglobulin tests are performed on the minor side in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it

Haemophilus influenzae in otitis media...

a valid concern



In many areas of the country, increasing numbers of *H. influenzae* show resistance to conventional antibiotic therapy.[1-3]

Ceclor is effective in the treatment of otitis media†, including that due to some ampicillin-resistant strains of *H. influenzae*.[4-9]

Ceclor has been shown to be clinically and bacteriologically effective in treating otitis media due to susceptible organisms.[10]

Ceclor is available in two pleasant-tasting liquids.

Ceclor provides effective single-agent antibiotic therapy for otitis media.

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

†Due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes*.

125-mg/5-ml and 250-mg/5-ml oral suspensions

Ceclor®

cefaclor

should be recognized that a positive Coombs test may be due to the drug.

Ceclor ® (cefaclor, Lilly) should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below:

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0703790]

References

1. J. Pediatr., *92*:889, 1978.
2. J. Pediatr., *94*:983, 1979.
3. J.A.M.A., *239*:320, 1978.
4. Antimicrob. Agents Chemother., *11*:470, 1977.
5. Antimicrob. Agents Chemother., *13*:584, 1978.
6. Antimicrob. Agents Chemother., *12*:490, 1977.
7. Current Chemotherapy, *II*:880, 1978.
8. Antimicrob. Agents Chemother., *8*:91, 1979.
9. Antimicrob. Agents Chemother., *13*:861, 1978.
10. Data on file, Eli Lilly and Company.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Lilly

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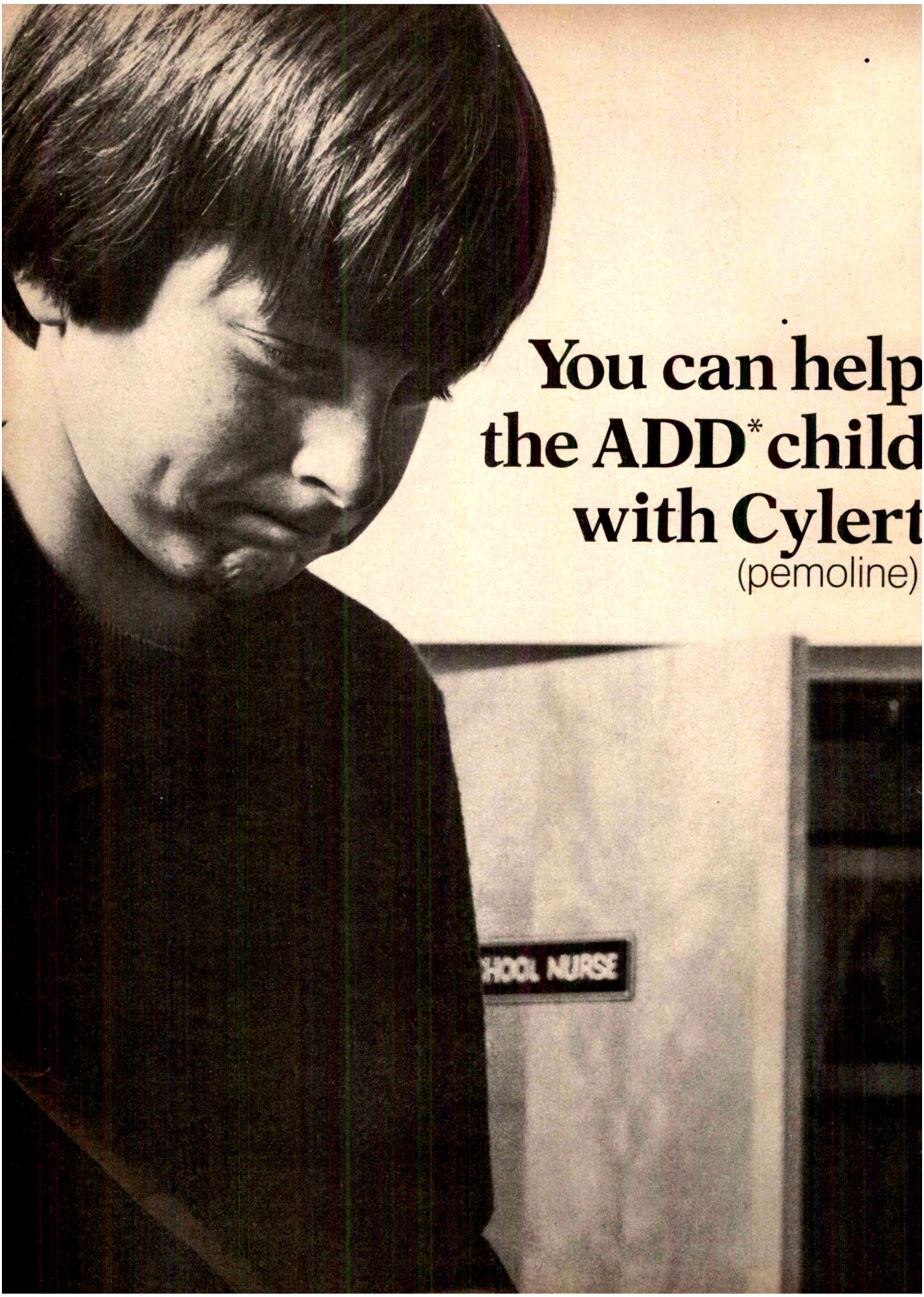
Carolina, Puerto Rico 00630



You can help the ADD* child with Cylert
(pemoline)

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Impressive all-day control.

Cylert works extremely well, given an adequate period of trial. Single daily doses are as effective for behavior control as multiple doses of methylphenidate or amphetamines. Blood levels are well sustained, without necessity for multidose administration.

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Cylert avoids problems of taking a drug at school. No involvement of school personnel. No peer teasing about noon-time dosing. The parents manage all medication, and the child carries no drugs. (And note that Cylert is Schedule IV, not II.)

Cylert® (pemoline) C IV

18.75, 37.5, 75 mg tablets; 37.5 mg chewables

Just once a day. At home.

*ADD: Attention Deficit Disorder (formerly called MBD, Minimal Brain Dysfunction), or the Hyperkinetic Syndrome. Please see next page for Brief Summary.

ABBOTT

9083319

Cylert® (pemoline)

DESCRIPTION: CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one.

Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg./ml.) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg./ml.

CYLERT (pemoline) is supplied as tablets for oral administration.

CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT, a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Abbott, Pharmaceuticals, Inc.
North Chicago, IL60064, U.S.A.

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Letters to the Editor

Nutritional Osteomalacia

Sir.—We have read the article by Dwyer et al (JOURNAL 133:134-140, 1979) and have recently observed an adult case of nutritional osteomalacia similar to those presented.

Report of a Case.—A 25-year-old woman came to this hospital with a chief complaint of increasing bone pain in the lower back and hips, which caused difficulty in walking for one year. For the past eight years, she had been on a strictly vegan diet that also excluded fish. Soy products were her only dietary supplement. Her four children (from 11 months to 7 years of age) are also on the same diet. Since the birth of her last child, the patient has continued to lactate and admitted to a 7-kg weight loss in the past year. The patient was referred to the department of rehabilitation medicine due to severe muscle weakness, wasting, and lethargy. She walked with the aid of a cane.

Physical examination showed a 34-kg woman, with a pigeon chest, a left kyphoscoliosis, a positive Chvostek's sign, patellar hyperreflexia, and cephalotruncal disproportion. Dentition was poor and a positive Gowers' sign was noted. Roentgenograms showed the classic pseudofractures (Looser's lines) of the ribs, a widening of the symphysis pubis, mild osteoporosis, diffuse osteopenia, and cupping of the diaphyses of the long bones.

Laboratory findings showed the following levels: total serum calcium, 7.6 mg/dL; magnesium, 1.7 mg/dL; phosphate, 2.6 mg/dL; albumin, 3.9 g/dL; iron, 60.0 μg/dL, with total iron-binding capacity, 426 μg/dL; total serum protein, 6.6 g/dL; serum alkaline phosphatase, 216.4 mU/mL; and serum parathyroid hormone, 406 picogram equivalents (pe)/mL (normal, 163 to 347 pe/mL). Fat was also present in the fecal samples, as well as protein (+2) and ketones (+4) in the urine.

The history, physical examination, laboratory, and roentgenographic findings all point to a diagnosis of vegetarian osteomalacia secondary to inadequate diet, lack of exposure to sunlight, and persistant lactation. The patient discharged herself against medical advice, and hence the children could not be examined.

Comment.—We believe that a vegan diet, as described earlier, with soy substitution is inadequate to prevent metabolic bone disease in adults as well as in children.

PAUL ELINSON, DO
LAWRENCE M. NEUSTADTER
MICHAEL G. MONCMAN
Philadelphia College of Osteopathic Medicine
4150 City Ave
Philadelphia, PA 19131

Hyperglycemia and Sepsis in a Newborn

Sir.—The article entitled "Recurrent Hyperglycemia Associated With Sepsis in a Newborn" (JOURNAL 133:645-646, 1979) was of interest to me. We have also seen several cases of hyperglycemia associated with sepsis over the past several years. Most of these infants were receiving partial or total intravenous alimentation at the time of the sepsis. Our conclusion was that any infant who did not tolerate a previously tolerated glucose infusion was considered as having sepsis until proven otherwise.

I cannot accept the explanation offered by the authors for the hyperglycemia seen in sepsis: namely, an inadequate insulin response. I would suggest that sepsis, especially that caused by Gram-negative organisms, is associated with endotoxin release. General cellular metabolism is decreased at this time, as is glucose utilization; thus, hyperglycemia would result.

LLOYD I. KRAMER, MD, FAAP
The Fairfax Hospital
3300 Gallows Rd
Falls Church, VA 22046

In Reply.—Dr Kramer is correct in pointing out that hyperglycemia in neonates with sepsis may have multiple etiologic factors. We were unable to measure the possible contributing effects of human growth hormone, hydrocortisone, glucagon, or catecholamines. Cryer et al[1] measured these hormones in baboons with *Escherichia coli* sepsis. They concluded that an inadequate insulin response was sufficient to account for hyperglycemia in sepsis.[1] Our patient had serum levels of insulin of 11 μU/mL and 13 μU/mL when her serum concentrations of glucose were 314 mg/dL and 285 mg/dL, respectively. For these glucose levels one would anticipate a greater insulin response.[2] Since our patient was apparently incapable of greater insulin production, I must assume that her response was inadequate. However, I do not have the data to indicate if this inadequate response were the result of sepsis or of the immaturity of a 1.3-kg, 1-month-old, preterm infant.

THOMAS JAMES III, MD, FACP
3015 Brownsboro Rd
Louisville, KY 40206

1. Cryer PE, Herman CM, Sode J: Carbohydrate metabolism in the baboon subjected to Gram-negative (*E coli*) septicemia. *Ann Surg* 174:91-100, 1971.

2. Cornblath M, Schwartz R: *Disorders of Carbohydrate Metabolism in Infancy*, ed 2. Philadelphia, WB Saunders Co, 1976, pp 95-99.

In pediatric infections

Septra®

Each teaspoonful (5 ml) contains:
40 mg trimethoprim and 200 mg sulfamethoxazole

Suspension B.I.D.

Acute
Otitis
Media

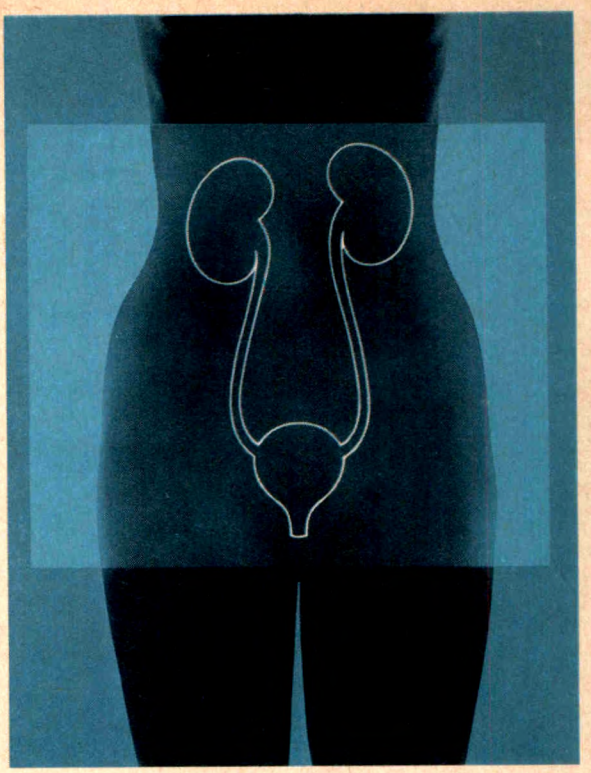
where the action is.

In acute otitis media

Septra Suspension provides effective antibacterial action against susceptible strains of H influenzae and S pneumoniae (D pneumoniae), the pathogens most likely to cause acute otitis media in children.

Septra Suspension is useful in many patients, but especially in those with penicillin allergy or with infections caused by ampicillin-resistant H influenzae. Limited clinical data are presently available on the effectiveness of treatment of acute otitis media with Septra when the infection is due to H influenzae resistant to ampicillin. However, in vitro data is highly favorable; when over 200 strains of ampicillin-resistant H influenzae were tested, all proved susceptible to TMP/SMX.*

And unlike most other antibacterials for the treatment of acute otitis media, Septra Suspension is administered on a convenient b.i.d. dosage schedule. The cherry-flavored suspension is well accepted by children.



In recurrent urinary tract infections

Septra Suspension provides effective antibacterial action in urine and blood against susceptible strains of E coli, Klebsiella-Enterobacter and Proteus. Whether the infection centers in the kidneys or bladder, Septra Suspension maintains effective levels at the site of the infection with just two doses a day.

Adequate fluid intake should be maintained and frequent urinalyses with careful microscopic examination performed during Septra therapy. Septra is contraindicated in infants under two months of age.

*In vitro data do not necessarily correlate with clinical results. Data on file, Burroughs Wellcome Co.
NOTE: Septra should not be used in the treatment of streptococcal pharyngitis.

Please see prescribing information on next page.

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

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Septra® DS B.I.D.

Each tablet contains: 160 mg trimethoprim and 800 mg sulfamethoxazole

Septra® DS Tablets Double Strength
Septra® Tablets
Septra® Suspension

INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: **For the treatment of urinary tract infections due to susceptible strains of the following organisms:** *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.**

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: **For the treatment of acute otitis media in children due to susceptible strains of** *Haemophilus influenzae* **or** *Streptococcus pneumoniae* **when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to** *Haemophilus influenzae* **resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.**

SHIGELLOSIS: **For the treatment of enteritis caused by susceptible strains of** *Shigella flexneri* **and** *Shigella sonnei* **when antibacterial therapy is indicated.**

PNEUMOCYSTIS CARINII **PNEUMONITIS: For the treatment of documented** *Pneumocystis carinii* **pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.**

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septra may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septra is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose—every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	½
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1½
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII **PNEUMONITIS:**
The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose—every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	½
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1½
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Letter From Abroad

The Fate of the Special Care Baby Unit

London.—I hope I may be forgiven if I seem to be a little cynical about the proliferating number of nonevents like Nannies' Sunday, National Breast Feeding Week, and the International Year of the Child. The calendar is crammed to capacity with birthdays, anniversaries, remembrance days, feast days, fast days, and holidays of obligation of one kind or another, all clamouring for the usual cards, flowers, and platitudes. It cannot be denied that they often provide a praiseworthy charitable outlet but they can also be used for commercial exploitation and even Breast Feeding Week had its spin-off with spates of paperbacks, conferences, television time, and an entirely new range of ladies' lingerie—in fact, all the usual publicity gimmicks with the exception, surprisingly, of a few free samples. True charity seems to find expression throughout the year without the artificial confines of a few days or weeks, the designation of which probably brings little extra benefit. As far as 1979 is concerned, it will always be inscribed in my memory as the year in which my own endeavours in neonatal intensive care, patiently built up over many years, were destroyed overnight and reached their lowest ebb.

On a fateful midsummer's day, our proverbial English weather unleashed a torrential downpour of rain that breached the frail defences of the little flat roof of the 15-year-old temporary hut housing our Special Care Baby Unit. Here, it is necessary to underline a fundamental difference between England and America where the vagaries of the weather appear to occasion neither surprise nor consternation. With us, unfortunately, it is well known that a half inch of snowfall is enough to paralyse the whole country, bringing chaos to roads, railways, telephones, water supplies, and a good many working activities not even remotely connected with ice or snow. It is simply a question of preparedness, like sweeping out gutters occasionally so that they are not overwhelmed by the first heavy shower of rain, causing enormous damage to electric fittings and costly equipment. Thus, our Special Care Baby Unit was hastily evacuated to a single room on our sick children's ward, an exodus worthy of Noah, complete with monitors, ventilators and faith. I, for one, believe implicitly that neonatal intensive care has enhanced the quantity and quality of its survivors.

The desperate search for a new home seemed at an end when we found a vacant space that might have been purpose-built for our needs. I imagine Brigham Young might have felt the same when he came upon the land of Salt Lake City. There were three empty nurseries with various side rooms in the very maternity hospital providing most of our referrals. The reasons for our separation from our obstetric colleagues go back into a long and convoluted history and the siting of a special care baby unit in a building in which no babies were ever born has long been a source of regret. We had evolved a transport system that was probably the first in the world and of which we were justifiably proud but often felt that if our Creator had intended obstetricians and paediatricians to work several miles apart, He would surely have furnished us with an umbilical cord longer than 35 cm.

We now had the nurses, the equipment, and the space. All that remained was the money to put in piped oxygen and to make a few minor alterations. It seemed little to ask but we are currently lurching through yet another financial crisis and the prospects of any contribution from the hospital budget stood at absolute zero. Then a leading children's charity—quick to grasp the immense benefit to mothers and babies—stepped in with a magnificent offer of nearly $100,000 to cover the cost. In the flush of success, thoughts gaily turned to the not far-off opening ceremony and which member of the Royal Family might agree to officiate. Little did we guess the problems ahead.

The first hurdle concerned the junior medical staff. Our junior doctors aim to work one night in three and no rearrangement of staff rotas would have made it possible to operate a special care baby unit in another building without at least one extra house-officer. After four months of wrangling, soul-searching, and sacrifice, this was eventually agreed. The next bombshell came in the form of an official missive to the effect that gifts to the National Health Service, the envy of the world, were not necessarily welcome no matter how well meant or munificent. It all depends on the "revenue consequences," the very thought of which strikes terror into the hearts of our administrators. The inevitable result is that it is now unbelievably difficult for generous people to give their money away to hospitals. Most donations have revenue consequences. Equipment needs bench space or floor space, it may have to be plugged in or, worse still, it may have to be serviced or repaired from time to time. Buildings need staff and staff need buildings. Even a fish tank needs an occasional change of water. We have just installed a computerized axial tomography head and body scanner, thanks to the grit and determination of a few stalwarts and to private donations amounting to nearly $1 million, and then only on the condition that all running costs would be found from private sources too.

After a somewhat ungracious acceptance of the offer for the new special care baby unit, the haggle began as to who was to do the work. Our Works Department was quick to dictate how it was to be done without wishing to do any of it. Since the disastrous reorganisation of the Health Service in 1974, the Works Departments are their own masters and do not take orders from hospital administrators. A project team was appointed and the project predictably came to a grinding halt. As more and more people became involved, the scheme became increasingly unrealistic and costly. Month after month went by, inflation eroding the original value of the donation until it became impossible to contain the cost within it. The most simple and menial task was costed at three or four times the amount we would spend in our own homes, and indeed ten times the cost of doing it ourselves. Offers of free paint, glass, and electric fittings were of no avail since painters and electricians were going to get their profits on these items whether we got them free or not. Add to this the subcontractors' profits, the main contractor's profit of another 15%, an inflation allowance, and a contingency allowance, and the scheme is soon priced out of existence.

So the chess game went on. Attack and defence, fortunes swaying, pieces

sacrificed, and the board slowly clears. Few pieces remain, a couple of white pawns, a bishop, and two knights against two black rooks and a superior number of black pawns. But with the end of the struggle in sight, a new threat has appeared.

The financial limitations of a welfare state must be plain to any responsible taxpayer. It all has to be paid for sooner or later and the noble concept of free health care cannot command a bottomless purse. This elementary truth is often lost on a vociferous minority that is least ready to lend its services for anything less than the going rate, let alone free. The writing has been on the wall for many years and this year's new government is committed to the electorate in bringing about a long overdue reduction in public spending. The big axe is beginning to fall and at last people are waking up to the realities of life. Our hospital has been told to spend $3 million less than last year. With inflation running at 10% to 15%, new wage awards, increased fuel costs, and expanding demands on most departments, the task would seem impossible. As yet, the axe has still to fall on the really basic cause of all our ills, overmanning. We have an entire tier of administration that could disappear overnight without any sense of loss. Wages and salaries are the largest item in the balance sheet but the slightest whisper of redundancies is enough to blow an industrial volcano, and so the axe is busily cutting patient services instead. A hospital here, a department there, a unit elsewhere. Our administrators—ironically the very tier we could so well do without—have drawn up a shopping list of proposed closures.

Heading this list is the closure of the Special Care Baby Unit. Second is the temporary closure of my colleague's Child Development Center. In just under two weeks, a group of worthy people will decide whether we can afford neonatal care for babies who will be born come what may. It is 15 months from the day that the rain came down and a year after we saw manna from heaven.

And so endeth the Year of the Child.

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60 YEARS AGO IN THE AJDC

Prognosis in Operated Cases of Hypertrophic Stenosis of Pylorus

In a 4½ year period from Jan 1, 1915 to July 1, 1919, one hundred and sixty-three infants had a pyloromyotomy at the Babies' Hospital of New York. Of these 133 were males, 30 females. Duration of symptoms prior to operation ranged from one week or less (twenty cases) to over five weeks (twenty-nine cases). Of the total, 106 had been breast fed, 57 artificially fed. Weight loss prior to operation ranged from 10 to 20 per cent. (fifty cases) to over 30 per cent. (twelve cases).

The mortality of operated cases varied considerably dependent on a number of factors:

	Mortality, %
Total mortality 32/163	20
Sex	
Male	22
Female	10
Duration of symptoms	
less than 4 weeks	13
more than 4 weeks	35
Type of feeding	
Breast	11
Artificial	35
Weight at time of operation	
less than 7 pounds	28
greater or equal to 7 pounds	9
Percent of weight loss	
Breast fed 0 to 10 per cent.	0
10 to 20 per cent.	3
20 to 30 per cent.	28
Artificial 0 to 10 per cent.	0
10 to 20 per cent.	23
20 to 30 per cent.	45
more than 30 per cent	60

The authors observe: "It becomes evident that the operation per se is, perhaps, the least important factor in the mortality."—Alton Goldbloom, MD, Ralph C. Spence, MD, Babies' Hospital, New York (19:263, April 1920).

Books

Pediatric Trauma, edited by Robert J. Touloukian, 646 pp, with illus, $39.50, Somerset, NJ, John Wiley & Sons Inc, 1978.

This book is a welcome addition to the literature. It is one of the few collections addressed exclusively to pediatric trauma. The potential audience for the book is quite large because accidents are a common cause of morbidity in childhood and are the leading cause of mortality, and because good, comprehensive textbooks dealing with the subject are not already on everyone's shelf.

The book is divided into two sections and contains 20 chapters. Part 1 includes seven chapters grouped together under the heading "General Considerations"; part 2 considers specific injuries by organ system.

The "Table of Contents" is impressive for two reasons. First is the roster of authors. Second, the editor must be credited for thoroughness and thoughtfulness in his selection of topics. This is particularly evident in the general considerations section. There are the more or less expected chapters (overview of pediatric trauma, evaluation and initial management, and anesthesia and intensive care); in addition, there are chapters on the psychologic aspects of physical trauma, radiologic considerations, birth injury (written jointly by a surgeon and a neonatologist), and the battered child syndrome. Specific areas addressed in part 2 are injuries to soft tissues, brain and spinal cord, the eyes, the heart and thorax, vessels, the abdomen, the kidneys, the lower urinary tract and perineum, the skeleton, hands, and skin (burns).

The photographs are of exceptionally high quality and are plentiful. In the chapter on the injured hand, for example, more than half of the 45 pages (excluding the three-page bibliography) are given to the presentation of 57 photographs.

Pediatric Trauma is in no way a manual to provide instantly to physicians and surgeons the necessary competence to manage injured children. The chapters are long and comprehensive, with consideration of pathophysiology and history. It is a book to be used for reference, but the writing style of several chapters suggests that the authors intended them to be read as well as referred to. And, unlike the "major" pediatric and surgical texts, this volume is not unwieldy in size or weight.

The authors of various chapters lean heavily on the experience gained at their own institutions. This creates problems only in the first chapter (overview of pediatric trauma), in which diagrams are labeled with abbreviations that may not be understood by persons outside the Baltimore community; even in the first chapter, however, the personal references do not detract from the teaching messages, and, in most instances, they are helpful.

Pediatric Trauma is a multiauthored text that, like all such works, has problems and successes relating to the number of contributors. An obvious consideration is that persons who are considered experts in their particular field are able to concentrate on only their own area. On the other hand, complication and contradictions are a potential problem. In many places in this book, the hand of the editor is clearly evident, guiding the reader from one chapter to another, as is appropriate and appreciated. There are, however, lapses in the editing that result in confusion and, possibly, serious error. Most notable are recommendations for similar therapy given in one chapter on a dose-per-pound basis and in another chapter on a dose-per-kilogram basis; the reader should not be forced to make such adjustments (nor depended on to do so). Also, the recommendations are not necessarily consistent from one chapter to the next, reflecting (accurately) that many points in management of trauma are guided by personal preference. For example, the management of seizures complicating craniocerebral trauma is addressed in two parts of the book, in the chapter entitled "Evaluation and Initial Management," and in the chapter on craniocerebral trauma. One author proposes vigorous treatment with intravenous amobarbital sodium, with a dosage as high as 5 mg/lb. He notes that, in addition, phenytoin, 2 mg/lb intramuscularly, should be given immediately followed by 1 mL [sic] per pound every six hours. Phenobarbital should be avoided because of its depressive effect. The other author states that phenobarbital is a good choice and lists his reasons for selecting this drug. The initial dose he recommends is 2 mg/kg with a daily dose of 4 to 6 mg/kg. This author does concede that short-acting agents such as amobarbital sodium may be used to treat a convulsion that is in progress, but no dosage is given, and there is no cross-reference to the earlier recommendation that includes a dosage. In addition to the editing problems in this example, one may also question the content: phenytoin is poorly absorbed from intramuscular sites and the intramuscular route should not be considered a preferred means of administering this drug; the doses of phenytoin and phenobarbital recommended for initial administration are insufficient to achieve a therapeutic level, so several doses over a prolonged period would be required before a patient would optimally be protected against seizures.

To whom will this text be of value? "More and more," the editor states in the preface, "the properly trained pediatrician must assume the role of the 'team captain,' particularly during the most important early days of management, and be fully aware of how to work up and assess the injured child. Furthermore, many minor injuries, if appropriately treated by their primary physician, never require a surgeon." The chapters vary in the success with which they address the nonsurgeon, however. This may be why the editor chose to address initial management of injured children in a separate chapter near the front of the book. One may well disagree with the author of that chapter about certain specific recommendations, but the general approach presented is excellent and well worth the time for anyone (nurse, physician's assistant, medical student, house officer, physician regardless of specialty) who will participate in the management of an injured child. The discussion of burns is also divided into two chapters, separating initial management and special ongoing care, and giving full attention to both.

There is emphasis throughout the book on the ways in which pediatric trauma differs from adult trauma, ways in which the injuries differ, the host responses differ, the patterns of injury differ, the physician's approach should differ, management differs, etc. The book is therefore valuable for emergency room teams used to dealing with adult patients and who are called on from time to time to assist injured children; they would be wise to consult this volume before extrapolating from their experience with adults.

Pediatric Trauma is now *the* reference text on the subject and as such should be available for consultation by physicians and nonphysicians preparing to participate in the management of injured children. Emergency room staff, pediatric surgeons and their trainees, and selected pediatricians and surgeons will glean a deeper understanding of pathophysiology and, based on recommendations in the text, will be able to develop an approach to injured children. Persons in the surgical subspecialties who deal with injured children will also find this a valuable resource. One reminder, however: using this book is not easy; it does not offer a shortcut approach. It requires time, attention, and thoughtful evaluation—but, then, so does the injured child.

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Pediatric Nutrition Handbook, edited by Donough O'Brien and G. B. Forbes, 472 pp, Evanston, Ill, American Academy of Pediatrics, 1979.

This comprehensive handbook is geared primarily to physicians involved in infant and child health care, in recognition that most medical schools and hospital teaching centers give insufficient attention to nutrition as an integral part of health care. There are 38 chapters, covering basic nutrition, assessment of nutritional status, nutritional needs and feeding of infants and young children, availability of community nutrition services and food assistance programs, and clinical applications. The last section covers a wide variety of common clinical problems, as well as some that are relatively rare. Finally, there are several chapters grouped as "Miscellaneous Topics." This section includes nutritional aspects of vegetarianism, health foods and fad diets, megavitamin therapy, nutrition and athletic performance, and food additives. Included also are chapters on infection, immune mechanisms, and the relationship between iron nutritional status and incidence of infection in infancy (which might just as well have been incorporated into the section on clinical applications).

Twenty-eight authors contributed to the handbook, and some sections are reprints of previous statements of the American Academy of Pediatrics (AAP) Committee on Nutrition. The style varies, as would be expected, but does not deter from the overall usefulness of the book. For the most part, greater attention is given to the problems most commonly encountered by pediatricians in practice. Less attention, rightly, is devoted to situations requiring the services of specialists.

There are any number of minor points with which one might take issue. As an example, the term "recommended dietary allowance" is used appropriately in the text, whereas "daily requirement" is used in a table (which, by the way, concisely summarizes useful information about the vitamins, thus saving needless pages of text). The interchangeable use of the terms "recommended dietary allowance" and "requirement" causes some gnashing of teeth among nutritionists (these terms are defined very differently by purists), but likely will not be noticed by most physicians. The only serious defect is the lack of an index, which would increase the usefulness of the book as a reference tool.

This book has been needed for a long time, and the AAP Committee on Nutrition should be applauded for providing this information in an easily available and readable form.

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Atlas of Abdominal Ultrasonography in Children, by Gary F. Gates, 283 pp, 109 illus (263 sonographic), $27.50, New York, Churchill Livingstone, 1978.

This *Atlas of Abdominal Ultrasonography in Children* is an excellent compilation of representative examples of abdominal ultrasonic images of childhood diseases. The atlas is organized into six chapters, with 109 figures composed of approximately 263 sonographic, 58 radionuclide scintiscan, 30 radiographic, and eight clinical and pathologic photographic pictures. The radiodiagnostic methods (scintigraphy and radiography) were corroborative and complimentary to ultrasonography. The quality of the sonograms, scintiscans, radiographs, and photographs is excellent. The sonograms are presented as black echos on a white background, hard-copy format.

Ultrasound is especially useful in pediatrics because it does not use ionizing radiation and because of its exopenetrant ("noninvasive") nature. The author uses the term noninvasive, which has been widely applied to ultrasound techniques despite the fact that sound waves are invasive or penetrant of tissues although apparently not injurious to them. To be effective in producing images, the sound waves must penetrate or invade tissues. This reviewer is suggesting "exopenetrant" as an alternative and possibly better term to more accurately convey the function of ultrasound. "Noninvasive," although a misnomer, is widely used and unfortunately has gained wide acceptance. "Invasive" imaging methods (use of guided catheters for angiography, use of radionuclides internally, etc) might be referred to as "endopenetrant" methods. The author emphasizes the ability of gray scale ultrasonography to demonstrate "normal or morbid anatomy" without dependence on organ function.

In chapter 1, general remarks include comparisons of ultrasound with other diagnostic methods, advantages of ultrasonography, and its limitations. A brief review is given of the various modes of sonographic scanning and general diagnostic criteria for cystic vs solid lesions. The problem of motion by the patient during sonography, the resultant needs for immobilization and occasional sedation are addressed. Proper attitudes for relating to children and their parents are emphasized in conjunction with specific scanning techniques in working with children.

Chapters 2 through 6 are concerned with specific abdominal organs or locations. Ninety-four relevant references through 1977 are offered, specific to each chapter. All of the 109 figures are accompanied by legends that contain abbreviated clinical in-

formation. In general, the author is successful in his purpose for writing the book and preparing this atlas although "Clinical Implications" might have been better offered in a more organized format within the text.

Overall, this atlas is a relevant source book regarding pediatric abdominal ultrasound. It should be useful for radiologists and ultrasonographers involved in the application of this relatively new and important diagnostic method to childhood abdominal diseases.

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Corporal Punishment in American Education, edited by Irwin A. Hyman and James H. Wise, 471 pp, $25, Philadelphia, Temple University Press, 1979.

In 1977, two youths severely beaten by their junior high school principal brought before the US Supreme Court the controversial issue of corporal punishment. The resulting Ingram vs Wright decision sparked a furor in American education. The highest court of the land ruled that corporal punishment as a disciplinary tool does not violate the Eighth Amendment prohibition of cruel and unusual punishment. Two years after the Supreme Court ruling, Irwin Hyman and James Wise, in their compendium *Corporal Punishment in American Education,* have attempted to sift through the complex, multidisciplinary array of questions corporal punishment raises. However, as they state in their foreword, theirs is no dispassionate examination of the issue; it is a statement of the need for and search for rational alternatives, which is meant to inform the discussion in light of the Supreme Court ruling. The book is organized into eight sections, including historical perspectives, legal perspectives, causes and consequences, case studies, surveys and opinions, research, and alternatives. The articles range from polemical to informative, with most being somewhere between.

The book's strengths stem from the editors' selection of a wide variety of sources to make their case. There are, after all, no hard data explicitly concerned with corporal punishment; and as we draw and extrapolate from related research, such as laboratory studies on the effects of punishment and aggression and discussions of child abuse and juvenile delinquency, we begin to appreciate the complexity of the issue. Although some of the articles considered in isolation are weak, as a collection they make a compelling argument. Thus, Williams' historical essay documenting that corporal punishment has always been woven into the fabric of American society is substantiated by Reardon and Reynolds' Pennsylvania attitude survey that indicates strong present-day acceptance of the use of corporal punishment. More provocative but methodologically troublesome is Bellak and Antell's cross-cultural data suggesting a link between societies that condone corporal punishment in their schools and levels of aggression found in children's free play.

Research on the effects of punishment is also reviewed. Bongiovanni suggests that punishment works in the short-term—it does lead to the cessation of behavior. In fact, considering only the short-term, Wise remarks that punishment may be more effective than reward. However, its long-term effects are pernicious: corporal punishment perpetuates itself in a variety of violent behaviors. Other research cited suggests relationships between corporal punishment and juvenile delinquency, child abuse, and aggression. But at the crux of the issue and not recognized by the editors is that corporal punishment is a moral issue as well as an empirical question of effectiveness. Even if research were to prove corporal punishment an efficacious means of behavior control, I would still object to its use, since it violates the dignity of the individual and instructs impressionable children that force is an acceptable means of problem-solving.

Given the editors' stated goals, it is a shame that the book devotes so much space to convincing the reader of the evils of corporal punishment and so little space to alternatives. The reader who wades through the volume in sympathy with its basic premises will be disappointed by the small number of solutions this collection provides. The section on alternatives embodies many of the flaws of the book: unfortunately, there are too few concrete suggestions and thoughtful proposals. Although the book's intent is to counterbalance the effect of the Supreme Court's decision by proposing alternatives to physical punishment, these last few essays do not fulfill the book's promise.

For those deeply concerned with the issue of corporal punishment, this book provides a good introduction to the issue and raises provocative questions about relationships between corporal punishment and violence. However, a practitioner will not glean much practical knowledge from its pages.

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Pediatric Hematology-Oncology, by Philip Lanzkowski, 432 pp, New York, McGraw-Hill Book Co, 1979.

Dr Lanzkowski calls his new textbook of hematology-oncology "a treatise for the clinician," and it seems to fit this description well. The book is not presented as an encyclopedic text of pediatric hematology-oncology. Rather, it presents a practical clinical approach to the differential diagnosis of hematologic disorders. The book was written to appeal particularly to the medical student, to the student of pediatric hematology-oncology, and to physicians practicing clinical pediatrics. It is easy to read and well indexed, and it includes a large number of tables. In this regard, Dr Lanzkowski has gone to great lengths to tabulate and summarize large blocks of data for concise presentation. This type of presentation is a great aid to the busy clinician or haggard house officer who lacks the time or inclination to read extensive discussions in the text.

The first ten chapters include disorders of RBCs, WBCs, and platelets. There is an additional chapter about blood coagulation and a final chapter on pediatric oncology. The oncology chapter constitutes about 25% of the total volume of this book.

The text, although readable, is not as well organized as the tabular material. This seems more related to the typesetting than to the structure of the presentation. For example, in the chapter regarding anemia in the neonatal period, the subheadings for hemorrhage, hemolysis, and failure of RBC production are inconsistent in format. Further, other headings and subheadings are difficult to follow in this and other chapters and diminish

the ease of locating material.

One of the strengths of the book is the chapter about iron deficiency anemia. Dr Lanzkowski has compiled a comprehensive review of iron metabolism. Tables are devoted to the etiology, the systemic effects, and the differential diagnosis of iron deficiency. Appropriate emphasis is given to those disorders wherein iron is lost through bleeding as well as those where intake of iron is deficient. Clinicians should find this chapter useful.

In the chapter regarding hemolytic anemia, the author has tabulated the etiology of hemolysis in a classical way into those causes external and those intrinsic to the RBC. Again, the tables and diagrams are useful for investigating hemolytic problems. I would criticize only that many of the tests presented for the diagnosis of hemolysis are neither necessary nor commonly ordered. For example, fecal urobilinogen, carbon monoxide, hemopexin, methemalbumin, and even RBC survival are usually unnecessary in the evaluation of a hemolytic anemia. It would have been helpful to the practitioner to designate those tests that are most useful in differential diagnosis.

As in any singly authored book, there is a strong reflection of the author's opinions. For example, not all pediatric hematologists would agree with Dr Lanzkowski's recommendation for daily penicillin prophylaxis in all patients with sickle cell anemia. Such prophylaxis would be more appropriate for those patients with sickle cell who have defective pneumococcal opsonization, a problem that is not discussed. In addition, the risk of drug-induced G6PD hemolysis in sickle cell anemia is overemphasized since patients with sickle cell have a young RBC population that is relatively resistant to oxidant damage.

About 25% of the book is devoted to pediatric oncology and provides an overview of the malignant disorders of childhood. The tables and charts are particularly useful. Dr Lanzkowski has tabulated the conditions associated with a high incidence of malignancy, the prognostic factors in malignant disorders, and the toxicities of the commonly used chemotherapeutic agents.

In summary, Dr Lanzkowski has done a fine job of gathering, consolidating, and presenting hematologic information for the student and the practitioner. His book is one of the most convenient sources for hematologic information.

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Diagnosis of Viral Infections: The Role of the Clinical Laboratory, edited by David A. Lennette, Steven Specter, and Kenneth D. Thompson, 254 pp, Baltimore, University Park Press, 1979.

This little volume is a smorgasbord, with something for everyone's intellect to nibble on! It is a compilation of papers presented at a symposium entitled "Diagnosis of Viral Infections: The Role of the Clinical Laboratory," held in Philadelphia, Nov 9 to 10, 1978.

The practical role of the diagnostic virology laboratory is outlined at the outset in three separate chapters devoted to the hospital laboratory, the state laboratory, and the federal reference laboratory. The final chapter, "An Infectious Disease Viewpoint of Diagnostic Virology," is a companion piece to the introductory material. These chapters are particularly well written and extremely practical for pediatricians, as well as for laboratory scientists. Tables are provided that show the proportion of positive viral isolations from all clinical material. Results from Rochester, NY, Seattle, and Tucson, Ariz, indicate that it is possible to find a specific viral cause in 20% to 40% of the cases studied.

Not only can a high percent of cases be diagnosed, but results can be obtained rapidly. Dr Menegus writes that in Rochester, at least half of 480 viral cultures showed positive results by the seventh day and frequently as early as the first or second day. Dr Ray states that for the period 1976 to 1978, 71% of the preliminary reports were sent to the physician by the fifth day. Although diagnostic virology may, in the words of Dr Gershon, be like "a rebellious teenager" (not quite grown up), the practical services virology can provide for primary care physicians are delineated clearly.

The chapter by Dr Tom Smith on collection and transport of specimens is very timely. How to collect and send samples are the most frequent queries that I, as director of a clinical virology laboratory, am asked.

There are three clinically oriented chapters toward the end of the book, which contain a thorough discussion of acute viral CNS infections, a brief overview of congenital and neonatal infections, and a useful classification of viral respiratory syndromes.

The midportion of the book is devoted to particular laboratory techniques. I found the chapter entitled "The Role of Electron Microscopy in Diagnostic Virology" informative and refreshingly honest. Although written from the point of view of an experienced electron microscopist, the author was quick to point out that electron microscopy was not always the most apt technique. In other chapters, newer techniques of great promise, such as cell-mediated assays for specific viruses, enzyme-linked immunospecific assay (ELISA), and immune adherence hemagglutination were covered nicely.

As with all multiauthor volumes, the quality is uneven. Several chapters are mere forums in which authors present their preliminary research findings, which is neither pertinent for readers with a clinical background nor scientifically satisfying. Fortunately, the majority of the chapters are above reproach.

In conclusion, this book is excellent for laboratory physicians and scientists interested in establishing or improving diagnostic virology laboratories. Pediatricians with special interest in infectious disease would find the book a valuable addition to their professional library. Because the clinical chapters are particularly useful as a review of specific viral syndromes, and "how to use the virus laboratory" sections most practical, this book is a worthwhile reference for every hospital library.

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Clinical Management of Mother and Newborn, by Gertie F. Marx, 274 pp, $29.80, New York, Springer Verlag, 1979.

Gertie F. Marx, MD, an anesthesiologist at the Albert Einstein College of Medicine, has elicited the aid of 11 anesthesiologists, five pediatricians, three obstetricians, and one statistician, 18 specialists in all, in writing a

scholarly book devoted to the first days after birth. Good writing with an almost uniformly clear style shows that the authors, most of whom are from the New York City area, were chosen wisely.

The bulk of the book, including ten of the 15 chapters, is an update and review of neonatal physiology, pathology, and treatment. An outstanding example of the latter is a chapter by Ermelando V. Cosmi, Professor of Anesthesiology and of Obstetrics, University of Rome, on "Exchange Transfusion of the Newborn Infant." This chapter, with 128 references, is the first extensive writing on this subject that I have encountered by a specialist outside the field of pediatrics. The first three chapters in the book are concerned with "Maternal Postpartum Problems." There is a chapter entitled, "The Normal Parent-Newborn Relationship," which includes currently fashionable practices, such as bonding. A final chapter is concerned with "Maternal and Perinatal Mortality," in which figures from New York City are given. Although comparable data of such extensive proportions would be difficult to obtain on a national scale, this should have been attempted.

On reading the chapters concerned with neonatal physiology one is again struck with the fact that the early work of numerous worthy neonatologists is frequently ignored by many modern authors. Although it is true that recent references are most likely to be available when current papers merely confirm the work of such pioneers as Barcroft, Dawes, and Smith, it is regrettable that their work is not recognized, especially in books where references are not restricted.

This book should be available in medical libraries and it will be valuable to students and practitioners. It is nicely printed, with many tables and line drawings, and a few photographs. In relation to most medical books, its size is small, and even by today's standards its price is outrageous.

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Books in Brief

Human Milk in the Modern World, by Derrick B. Jelliffe and E. F. Patrice Jelliffe (500 pp, New York, Oxford University Press Inc, 1978) (price not stated). This book is a rich compendium of data on breast-feeding and the virtues of human milk for the feeding of infants both in Western society and in the countries of the third world. It provides plenty of arguments for those who want to promote breast-feeding, and it includes an abundance of practical information that should be of great help to nursing mothers and their physicians. Every conceivable argument in favor of breast-feeding, lactation amenorrhea, mother-infant bonding, antiinfective properties, economies, antiallergic properties, enhancement of iron absorption, lower incidence of neonatal hypocalcemia, etc, is discussed in considerable detail. Methods of promoting breast-feeding are presented.

The biochemical aspects of human milk are presented in somewhat less detail than one would have expected from a book of this size, and there is no discussion of the inadequacies of human milk for tiny premature infants (see Fomon, Ziegler, and Vasquez, this JOURNAL 131:463-469, 1977; Committee on Nutrition, American Academy of Pediatrics, *Pediatrics* 62:826-834, 1978). However, the main thrust of this book is the social and cultural aspects of breast-feeding, and the authors make a strong plea for an increase in this practice worldwide.

Growth and Development of Children, ed 7, by George H. Lowrey (464 pp, Chicago, Year Book Medical Publishers, 1978) (paperback, price not stated). The seventh edition of this well-known work attempts to present an overview of human growth and development in all of its aspects. New or greatly expanded material in this edition deals with placental development, prematurely born infants, maternal-child relationships, cognitive development, immunological and endocrinological phenomena, facial growth, and nutritional influences. It presents a balanced view of this aspect of biology, which is the hallmark of pediatrics.

Human Body Growth in the First Ten Years of Life, by Howard V. Meredith (141 pp, $4 [paperback], Columbia, SC, The State Printing Co, 1978). This brief work presents data on physical growth values for infants and children from various countries around the world. Data on dentition and on certain body proportions are also included. The main emphasis is the presentation of the data themselves and the comparisons of infants and children of various cultural and geographic origins. Lists of references are provided for readers who want more detail; however, they will have to look elsewhere for information on the processes that underlie the phenomenon of growth.

Secular Trends in Human Growth, Maturation, and Development, edited by Alex F. Roche. Monographs of the Society for Research in Child Development, serial No. 179, vol 44 (120 pp, $7 [paperback], Chicago, University of Chicago Press, 1979). Today's children are taller and heavier than their peers of yesteryear, and these so-called secular changes have been documented in many countries around the world and have involved all social classes. The articles in this monograph review these data, and they remind us that certain features of maturation, particularly menarche, are now occurring at an earlier age. Today's children also seem to be a bit stronger; thus, it should come as no surprise that Olympic records have steadily improved through the years.

Paediatrics and Growth, edited by Donald Barltrop (157 pp, London, Fellowship of Postgraduate Medicine, 1978) (price not stated). This book consists of articles read at the Fifth Unigate Workshop, held at the Royal College of Physicians in May of 1977, and it includes verbatim discussion by the participants. Here one will find an up-to-date discussion of the various factors and phenomena that are responsible for the growth process, including embryonic and fetal as well as postnatal growth. The role of somatomedin (a polypeptide that is growth-hormone dependent) is presented, and there is an interesting discussion of the role of the fetal brain in stimulating intrauterine growth. There are chapters on growth disorders. The presentations and discussions are at a high level, and fundamental concepts are emphasized. This little book should be of interest to all students of human growth.

GILBERT B. FORBES, MD
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WARNING

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

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Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy – Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Recent studies of erythromycin reveal that its use in patients receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In such a case, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

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Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

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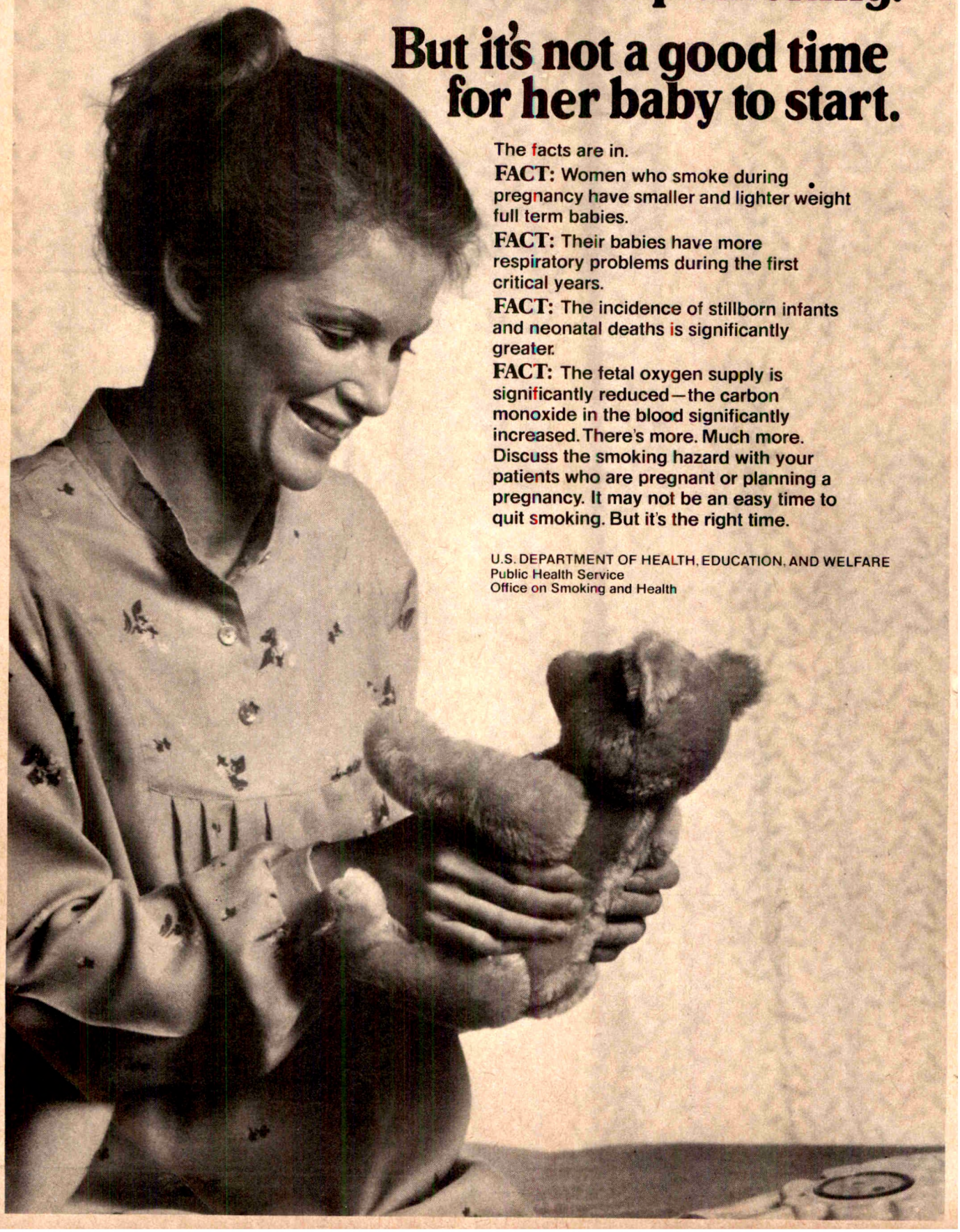

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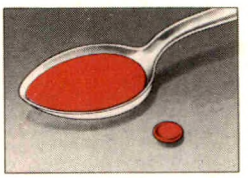

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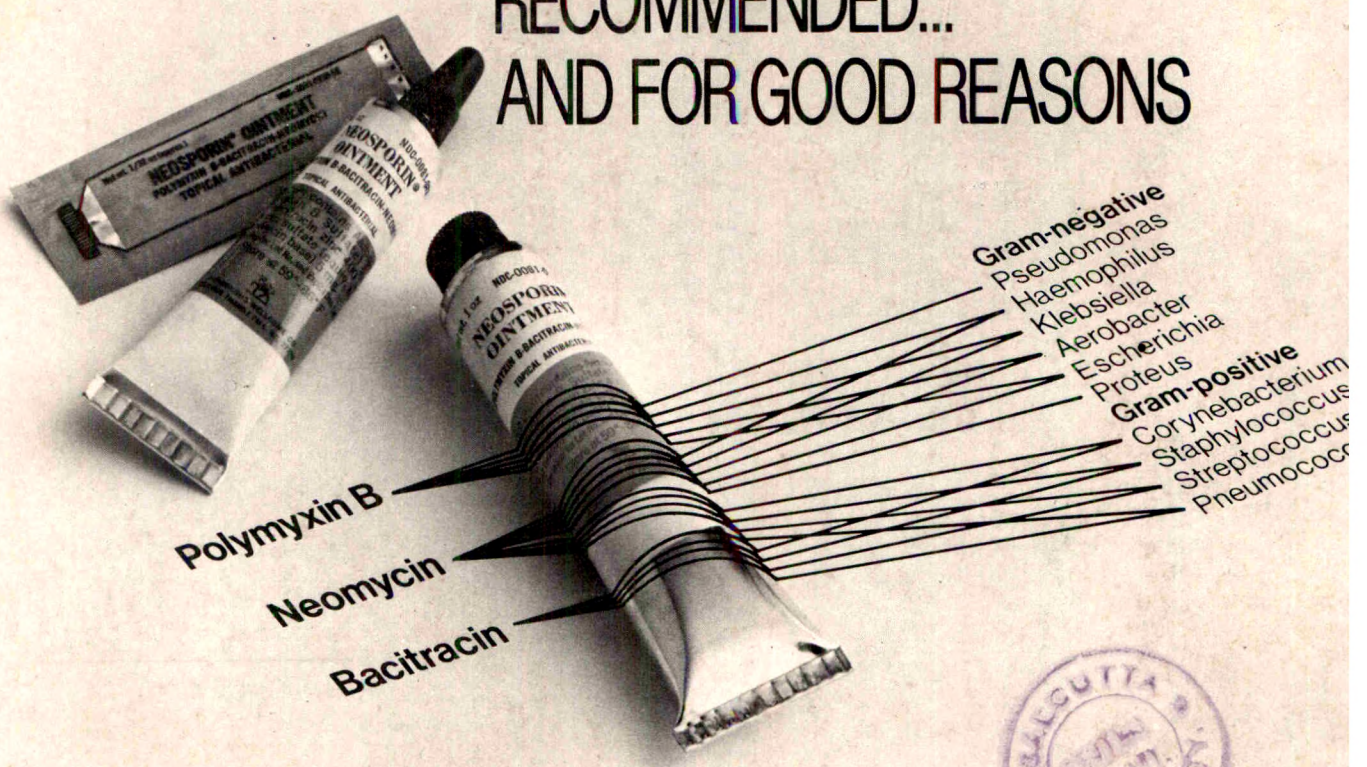

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

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Complete literature available on request from Professional Services Dept. PML.

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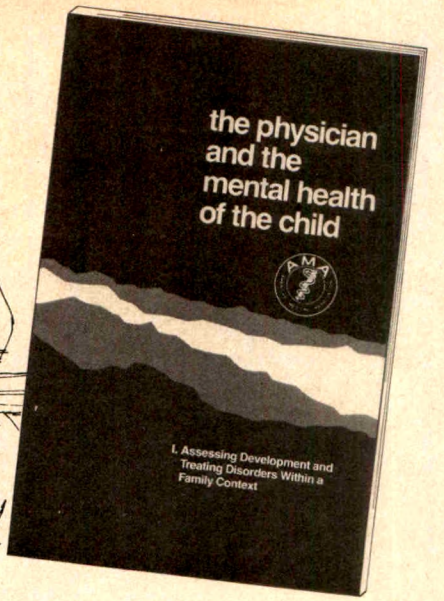

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Because any child must be seen as a developing human being and any pathology must be assessed in a developmental framework, much of this first monograph is devoted to developmental levels and problems and how they can be appropriately evaluated in the juvenile patient. Part I of the book gives both general and background material and overall information about children, as well as some "how to do it" details.

CONTENTS

Chapter I: Child and Family Assessment: The Family Inventory
A family inventory should be taken in addition to the medical history. The child who presents for treatment must be viewed in the context of the family of which he is a part: he cannot be viewed in isolation. A comprehensive family inventory helps to identify developmental problems in the child, while assessing the interplay of their multiple causes.

Chapter II: Assessing Developmental Levels
Chapter III: Developmental Tests
Developmental assessment should determine whether the child is progressing optimally in all regards, and, if not, the appropriate steps that can be taken to ameliorate problems and prevent serious pathology. Since the way a physician uses assessment procedures depends on training, experience and the extent to which he wishes to be involved in screening, development and guidance, recommendations are offered to help a physician assess development in accordance with his capabilities and interests. A summary of commonly used developmental tests is included.

Chapter IV: Assessing Developmental Problems
Not only must the child's current level of development be evaluated, but his innate strengths and weaknesses, and how the environment has supported or impeded development, need to be determined. The physician must help the child and his family utilize their resources and strengths to maintain health.

Chapter V: Assessing Parental Capabilities
Parental capabilities also need to be evaluated. If the physician believes there may be problems in the parent-child relationships, this concern should be shared with the parents in a non-judgmental and nonaccusatory way.

Chapter VI: Emotional Concomitants of Physical Illness
When formulating a treatment program for a child with emotional symptoms occuring primarily or secondarily with physical illness, the physician needs to consider the emotional reactions of the ill child. He should also be knowledgable about phase-specific developmental needs and tasks of the child; the individual personality characteristics of the child and parents; specific illness and treatment-based anxieties; and sociocultural characteristics of the family.

Chapter VII: Treating Children with Mental or Developmental Problems
The primary care physician should be familiar with the role of psychopharmacotherapy, environmental changes, supportive psychotherapy, behavioral modification, remedial education, marriage counseling and insight-producing psychotherapy, even if he does not wish to incorporate these psychological treatments into his practice. The dynamics of referral and consultation are also discussed.

Chapter VIII: Cultural Characteristics Affecting Patient Care
Chapter IX: Common Problems Affecting the Mental Health of Children in Non-Mainstream Families
Part II of *The Physician and the Mental Health of the Child* addresses the unique needs of the children in various ethnic groups, children coming from family situations and backgrounds largely unfamiliar to the average practicing physician—the urban poor, blacks, American-Indians, Mexican-Americans and single-parent families. The history of these families, their contacts with the health delivery system, particular developmental problems their children migh have and the appropriateness of the patterns of care they are now receiving are examined.

With the growth of third party payments, these patients will come increasingly to the attention of the primary care physician, who should be prepared to assess the impact of their cultural considerations and influences on the child's mental health. He should recognize also that particular ethnic groups may have unique patterns and problems.

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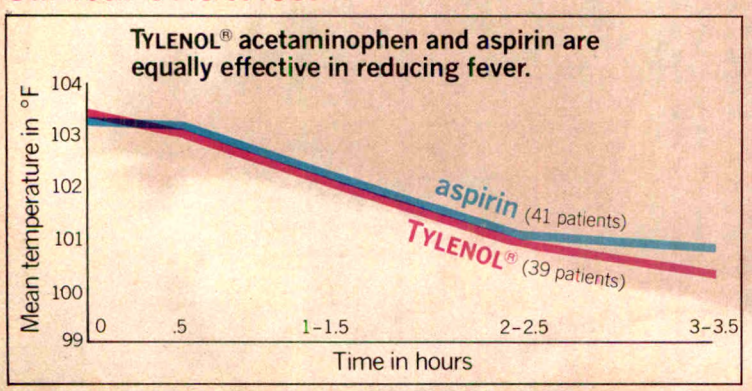

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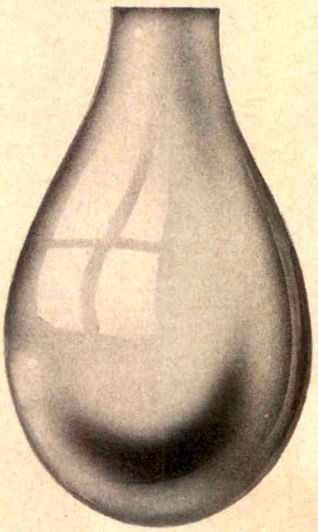

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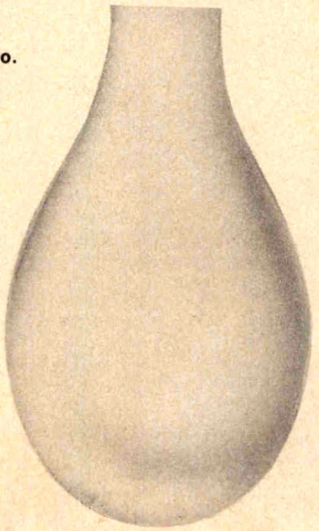

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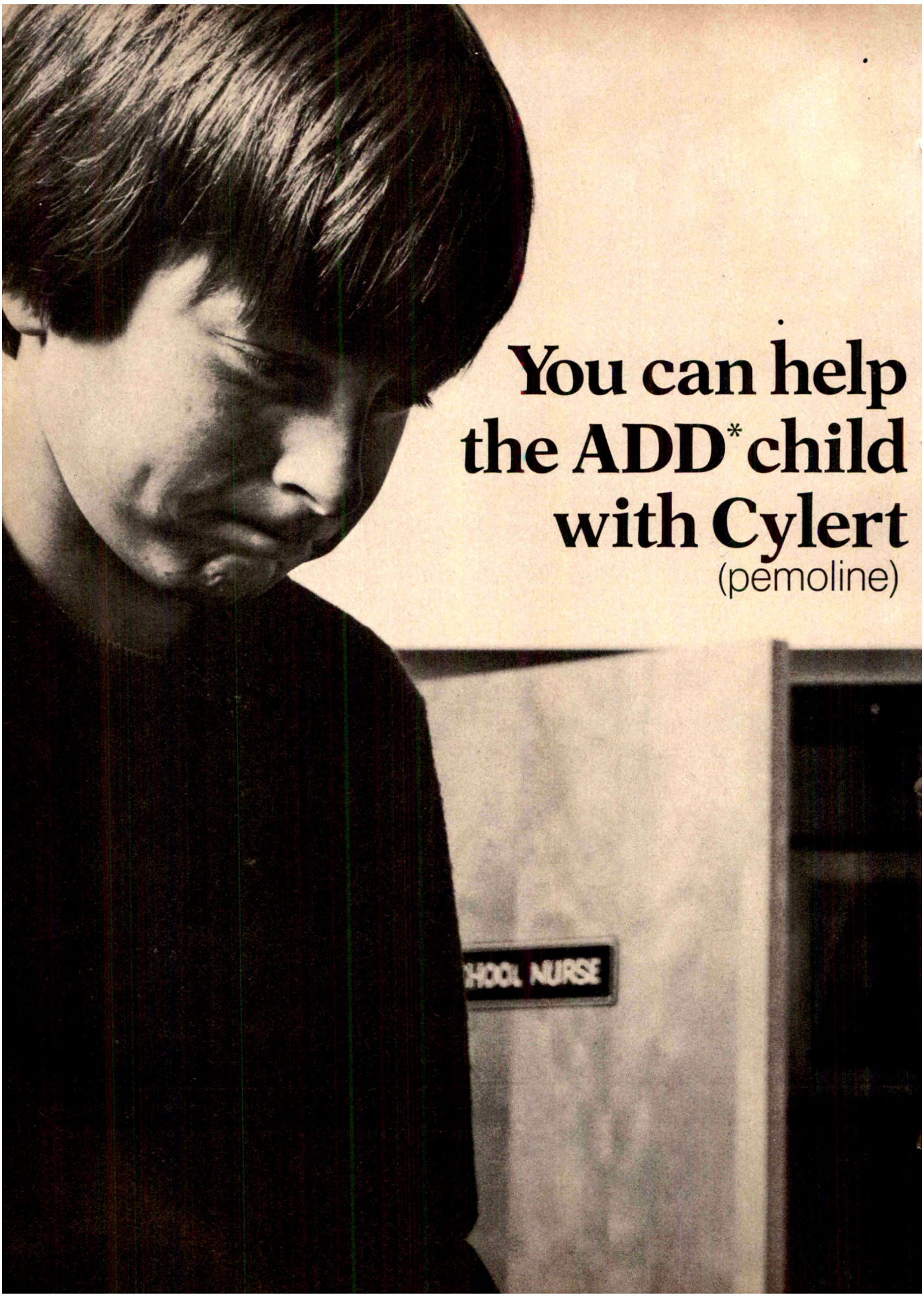

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DESCRIPTION: CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one.

Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg./ml.) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg./ml.

CYLERT (pemoline) is supplied as tablets for oral administration.

CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

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National Council on Child Health,[1] Ritalin was described as among the most effective and best-documented agents for stimulant therapy in hyperkinetic children.

Reduces hyperactivity, impulsive behavior

Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

Generally well tolerated

Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

***Attention Deficit Disorders:** new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

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TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Tablets, 20 mg (peach, scored); bottles of 100 and 1000.

Tablets, 10 mg (pale green, scored); bottles of 100, 500, 1000 and Accu-Pak® blister units of 100.

Tablets, 5 mg (pale yellow); bottles of 100, 500 and 1000.

Dispense in tight, light-resistant container (USP).

665382 C80-14 (1/80)

Consult complete product literature before prescribing.

References

1. Kugel RB, Scherz RG, Seidel HM, et al. Council on Child Health: Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4):560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al. Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30**:354-359.
3. MacKay MC, Beck L, Taylor R. Methylphenidate for adolescents with minimal brain dysfunction. *NY State J Med* 1973 (Feb.); **73**:550-554.

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Inhibition of Iron Absorption by Certain Foods

The article of Oski and Landaw (see p 459) and the recently published report by Saarinen and Siimes[1] indicate that the timing and choice of solid foods for infants may have a much greater influence on iron nutrition than was previously realized. In early infancy, most of the demands of iron for growth are supplied by relatively abundant neonatal iron stores, and absorption of food iron plays a subsidiary role.[2] As neonatal stores become depleted after about four months in the term infant, iron must be supplied almost exclusively from dietary sources. The transition between these two phases of iron metabolism coincides with the time when the introduction of solid foods is currently recommended.[3,4]

Absorption of food iron is under two major influences: the first is the homeostatic function of the intestinal mucosa, by which the absorption of iron increases as iron stores decrease; second and less widely appreciated is the interaction of food iron with other dietary constituents. This interaction plays as important a role as the actual iron content of the diet.[4] Oski and Landaw measured the absorption of iron in a group of adult subjects from breast milk alone and breast milk fed with strained pears. The absorption from breast milk alone was about four times greater than when breast milk was administered with pears at the same time. Despite the fact that breast milk contains only a small amount of iron (0.5 mg/L during the first month after birth, decreasing to about 0.3 mg/L when the child is between 4 and 6 months of age),[5] the percent absorbed has a significant impact on iron nutrition because milk accounts for almost all of the infant's diet during this period. Studies of infants fed primarily breast milk show that an average of about 50% of the iron in breast milk is absorbed,[6] a remarkably high figure, compared with 12% from unfortified cow's milk formula.[7] The data of Oski and Landaw indicate that introduction of some solid foods in a breast-fed baby could compromise this excellent iron absorption. Similar conclusions emerge from the studies of Saarinen and Siimes,[1] who estimated the rate of increase in total body iron during the four-month period spanning the introduction of solid foods. When total body iron was calculated from hemoglobin concentration, serum ferritin, and body weight, it was found that the rate of iron accumulation decreased in breast-fed infants when unfortified solid foods (primarily fruits and vegetables) were introduced.

The clinical implications of the two studies are fortunately in line with current recommendations for infant feeding, particularly in respect to the benefits of prolonging the duration of breast feeding[8] and delaying the initiation of solid foods.[3,4] The advantages of breast feeding have been discussed in a recent review.[8] However, it is worth emphasizing that there is a marked disparity between current recommendations and common practices.[9] Many of the advantages of breast feeding may not fully apply if it is maintained for only one or two months, as is commonly the case, rather than six months or more as recommended.[8] Similarly, numerous surveys indicate that well over half the infants have had solid foods introduced before two months of age,[10] whereas the introduction of solid foods is recommended between four and six months of age.[3,4] Although the excessively early introduction of some solid foods is likely to compromise iron absorption unnecessarily, the breast-fed infant does eventually require additional sources of food iron. After six months of age, the iron available from

breast milk alone is insufficient to prevent consistently the depletion of iron stores and some degree of iron-restricted hemoglobin production.[11]

What are some reasonable choices among infant foods that are likely to meet iron needs and are also consistent with good overall nutrition? Most of the relevant studies of iron absorption from individual foods and from mixed meals have been done in adults and have shown that the iron content of foods gives little indication of how much will be absorbed. The percentage of iron absorbed from individual foods varies over at least a 20-fold range.[12] Among individual foods, iron is best absorbed from meat and is less well absorbed from vegetable and dairy foods. The interaction of foods in each meal is also important and has a major effect on the iron absorbed from the meal as a whole. Iron absorption studies from composite meals indicate that meat and ascorbic acid will enhance absorption of iron from the *entire* meal, whereas milk and other dairy products have the reverse effect.[13,14] For example, the presence of meat, poultry, or fish resulted in the absorption of about four times as much iron from a standard meal as the substitution of equivalent portions of cheese, milk, or eggs.[13] Orange juice with a meal more than doubled the iron absorbed from the entire meal.[14] Two of the traditional sources of iron in the infant diet, spinach[12] and egg[14,15] (yolk) have been discredited. Although both foods are rich in iron, the iron is in a form that is not well absorbed.

It would be helpful to have more information about iron absorption from single foods and food combinations in infants. However, even with what is known at present, some feeding patterns can be favored over others. In terms of iron status as well as general nutrition, current recommendations for more prolonged breast feeding[8] and later introduction of solid foods[3,4] deserve support. Recommendations covering broader aspects of iron nutrition in infancy were discussed in a recent statement of the Committee on Nutrition,[16] but the influence of solid foods (other than iron-fortified cereal) received little attention. When solid food is started between about four and six months of age, iron-fortified dry infant cereal seems a good first choice.[16] In a Norwegian study, a form of iron-fortified cereal was shown to be effective in preventing iron deficiency in infancy[17] and more recent studies in infants suggest that the percentage of iron absorbed from cereal is in the same general range as the absorption of iron from iron-fortified cow's milk formulas.[18] It may prove beneficial in the future to fortify dry infant cereals with ascorbic acid in addition to iron, to enhance iron absorption. This is currently being done with weaning foods distributed by some international and bilateral agencies, eg, United States Agency for International Development.[19] After several additional solid foods have been gradually introduced, after 6 months of age it seems a good idea to offer one meal of solid foods a day that does not include milk but substitutes water or orange juice as a beverage. This meal could include both iron-fortified dry infant cereal and orange juice (or other ascorbic acid-rich food) or iron-fortified cereal and meat; fruit or vegetable could also be included.

There are a variety of options for avoiding iron deficiency in infancy.[16] In the term breast-fed infant, this type of dietary regimen should eliminate the need for iron drops. Similar considerations should apply to the selection of solid foods for term infants who are fed formula without added iron. Infants who are fed iron-fortified formula have an ample supply of iron, and are less dependent on additional iron from solid foods. Any of these alternative feeding regimens should successfully bridge the period of tenuous iron balance during late infancy.

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References

1. Saarinen UM, Siimes MA: Iron absorption from breast milk, cow's milk, and iron-supplemented formula: An opportunistic use of changes in total body iron determined by hemoglobin, ferritin, and body weight in 132 infants. *Pediatr Res* 13:143-147, 1979.

2. Dallman PR, Siimes MA, Stekel A: Iron deficiency in infancy and childhood. *Am J Clin Nutr* 33:86-118, 1980.

3. Committee on Nutrition: On the feeding of supplemental foods to infants. *Pediatrics*, to be published.

4. Fomon SJ, Filer LJ Jr, Anderson TA, et al: Recommendations for feeding normal infants. *Pediatrics* 63:52-58, 1979.

5. Siimes MA, Vuori E, Kuitunen P: Breast milk iron: A declining concentration during the course of lactation. *Acta Paediatr Scand* 68:29-31, 1979.

6. Saarinen UM, Siimes MA, Dallman PR: Iron absorption in infants: High bioavailability of breast milk iron as indicated by the extrinsic tag method of iron absorption and by the concentration of serum ferritin. *J Pediatr* 91:36-39, 1977.

7. Saarinen UM, Siimes MA: Iron absorption from infant formula and the optimal level of iron supplementation. *Acta Paediatr Scand* 66:719-722, 1977.

8. Committee on Nutrition: Breast feeding. *Pediatrics* 62:591-601, 1978.

9. Fomon SJ: What are infants fed in the United States? *Pediatrics* 56:350-354, 1975.

10. Fomon S: *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974, p 16.

11. Saarinen UM: Need for iron supplementation in infants on prolonged breast feeding. *J Pediatr* 93:177-180, 1978.

12. Layrisse M, Martinez-Torres C: Food iron absorption: Iron supplementation of food, in Brown EB, Moore EV (eds): *Progress in Hematology*. New York, Grune & Stratton Inc, 1971, vol VII, pp 137-160.

13. Cook JD, Monsen ER: Food iron absorption in human subjects: III. Comparison of the effect of animal proteins on nonheme iron absorption. *Am J Clin Nutr* 29:859-867, 1976.

14. Rossander L, Hallberg L, Björn-Rasmussen E: Absorption of iron from breakfast meals. *Am J Clin Nutr* 32:2484-2489, 1979.

15. Callender ST, Marney SR, Warner GT: Eggs and iron absorption. *Br J Haematol* 19:657-665, 1970.

16. Committee on Nutrition: Iron supplementation for infants. *Pediatrics* 58:765-768, 1976.

17. Moe PM: Iron requirements in infancy: Longitudinal studies of iron requirements during the first year of life. *Acta Paediatr*, suppl 150, 1963.

18. Rios E, Hunter RE, Cook JD, et al: The absorption of iron as supplements in infant cereal and infant formulas. *Pediatrics* 55:686-693, 1975.

19. *Commodities Reference Guide*, section 3: *Food for Peace, Agency for International Development*, Public Law 95-480, Title II. US Congress, 95th Congress, 1978.

New Thoughts on Aspirin

Aspirin continues to hold its place as a cheap and effective way of treating patients with juvenile arthritis. The article by Doughty and his colleagues in this issue (p 461) reiterates aspirin's effectiveness and gives us a number of practical points in its usage.

Although rheumatologists (and Jane Schaller recently for children[1]) have often pointed out the desirability of maintaining serum salicylate levels between 20 and 30 mg/dL, this report satisfactorily establishes these limits. Most important is the upper limit where the authors have shown that there is no significant improvement in clinical response with salicylate levels higher than 30 mg/dL. When other nonsteroidal anti-inflammatory drugs were not available for the treatment of juvenile arthritis, it was thought to be worthwhile to try to push aspirin levels higher than 30 mg/dL. However, with the availability of at least one of the newer agents, tolmetin sodium,[2] it probably is inadvisable to continue aspirin therapy if a child is not doing well at levels close to 30 mg/dL, or when aspirin toxicity appears within the therapeutic limits. In this study, 16% of the children were forced to stop aspirin therapy because of side effects. This is remarkably close to the number of patients who were withdrawn from an aspirin regimen in a double-blind study against a nonsteroidal anti-inflammatory drug where the aspirin withdrawal rate was 11%. In that study, aspirin was given at an average dose of 90 mg/kg. However, in the study by Doughty et al almost 30% of the patients required doses in excess of this level to maintain salicylate levels greater than 20 mg/dL (their lower limit). To further confuse this issue, Makela and her colleagues[3] reported that at dosages of aspirin in a range similar to those used in the Schaller[1] and Levinson et al[2] studies, salicylism appeared in about 50% of the patients. This may have been a peculiarity of their patient population since they also believed that maximum therapeutic levels should be close to 30 mg/dL (in their case, 27 mg/dL).

When all of these recent reports are digested, we can see that aspirin therapy in children with juvenile arthritis can be placed on a firm footing. It appears wise to start children at dosages not higher than 90 mg/kg. If compliance can be assured, a serum salicylate level obtained about two weeks after onset of aspirin therapy (to allow for equilibration) will provide a further clue to proper dosage levels. If the level is less than 20 mg/dL, then one should increase the dosage to about 100 mg/kg/day. Taking a repeated serum salicylate level after several weeks indicates whether the optimum therapeutic levels have been reached. If the level continues to be less than 20 mg/dL, then, as pointed out by Doughty et al, dosages greater than 100 mg/kg/day will be required; and this was necessary in 30% of the patients they treated. Nausea or vomiting may be an indication of hepatotoxicity, and liver function studies should be done if this occurs. These children, according to Doughty and his co-workers, could be receiving choline salicylate therapy with improvement in the liver chemistries and no recurrence of symptoms while still achieving adequate therapeutic salicylate levels.

It should be mentioned that recent reports show that in those children who are old enough to swallow tablets, enteric-coated aspirin may be a safer and easier way to give the drug. Gastroscopic studies in adults have shown that there is significantly less irritation of and ulcer formation in the gastric mucosa with the use of enteric-coated aspirin.[4] Serum salicylate levels achieved with this preparation were comparable to those achieved with regular or buffered aspirin. Orozco-Alcala and Baum[5] similarly showed that enteric-coated aspirin produced levels similar to those obtained with regular and buffered aspirin and also pointed out that there was a higher degree of acceptance in children with this preparation, which is easier to swallow because of the smooth coating.

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References

1. Schaller JG: Chronic salicylate administration in juvenile rheumatoid arthritis: Aspirin "hepatitis" and its clinical significance. *Pediatrics* 62:916-925, 1978.

2. Levinson JE, Baum J, Brewer E, et al: Comparison of tolmetin sodium and aspirin in the treatment of juvenile rheumatoid arthritis. *J Pediatr* 91:799-804, 1977.

3. Makela AL, Yrjana T, Mattila M: Dosage of salicylates for children with juvenile rheumatoid arthritis. *Acta Pediatr Scand* 68:423-430, 1979.

4. Silvoso GR, Ivey KJ, Butt JH, et al: Incidence of gastric lesions in patients with rheumatic disease on chronic aspirin therapy. *Ann Intern Med* 91:517-520, 1979.

5. Orozco-Alcala JJ, Baum J: Regular and enteric coated aspirin: A reevaluation. *Arthritis Rheum* 22:1034-1037, 1979.

Injuries in High School Physical Education Classes

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• **Suburban high school pupils participating in physical education classes sustained 3.6 injuries per 100 participants per year that were noted on official school accident reports, and 5.4 injuries per 100 for which pupils visited the school nurse. These latter injuries were minor. The official school accident reports indicated that injuries occurred at approximately equal rates in boys and girls; most were due to accidents that did not involve another participant or a piece of sports equipment, and, although usually not severe, were referred by the school nurse for further evaluation or treatment in some cases. Sprains were the most common type of injury and the ankle was the most commonly injured area. No particular set of conditions was identified wherein preventive measures could be taken to decrease the injury rate.**

(*Am J Dis Child* 134:456-458, 1980)

Although injuries of high school pupils associated with participation in organized sports have been well described,[1-9] similar information has not been reported for injuries associated with participation in physical education classes. We studied the incidence and characteristics of injuries of suburban high school pupils that were related to their participation in physical education classes.

SUBJECTS AND METHODS

The study population included approximately 1,870 predominately white, middle-class pupils who attended a suburban Pittsburgh high school between September 1976 and June 1978. Pupils were required to participate in physical education classes during two 56-minute periods each week. Approximately 1% of all pupils were exempted from physical education class for chronic medical problems or independent study programs, and about 6% were absent from class on an average day. The usual activity time in a physical education class, allowing for changing clothes and roll call, was approximately 40 minutes. Thus, a 36-week school year resulted in a maximum of about 48 hours of physical education activity.

In each segment of the school year, pupils were allowed to choose between several kinds of physical education activity. During unsuitable weather, sports such as basketball, volleyball, table tennis, and dodgeball were substituted for outdoor activities. Usual physical education activities included field hockey, soccer, softball, touch football, gymnastics, swimming, basketball, wrestling, volleyball, track, and racket sports. Because of variation in activities and variation in attendance, it was not possible to calculate accurately the number of participants or the hours of participation associated with specific activities.

Two sources of data were used: official school accident injury reports and health room records of the school nurse. Almost all official accident reports originated with the school nurse, who did not, however, use explicit criteria to decide which accidents were reported and which were not. Implicitly, based on more than 20 years of experience at the study school, the nurse judged (1) whether the pupil needed to be referred for further evaluation and care, and (2) whether the school, specific personnel, or another pupil might be considered liable for the accident. She completed accident reports in any of these cases. Most pupils for whom accident reports were filed were removed from physical education classes until their injury was fully evaluated.

The official accident reports contained the sex, age, and grade of the pupil; type of injury; body part injured; assumed cause of the injury; area of the school and activity in which the injury occurred; course of action taken (ie, referred for care, sent home, returned to class); and results of referral, if known. No explicit criteria were used for categorizing the injury (eg, contusion, sprain, laceration), though the diagnosis of fracture required roentgenographic confirmation. If two injuries were listed (eg, sprain and contusion), the injury considered to be primary (eg, sprain) was used in this study. The activity in which a pupil was engaged was classified according to specific sports and as to whether the injury involved the person only or involved others (eg, collision).

Officially reported accidents represented only a part of all physical education class-related injuries. The school nurse also saw a number of pupils for physical education class injuries that were not recorded on accident reports. Because school policy dictated that a record be kept of the complaint at the time of presentation and disposition of all visits to the nurse for any reason, information about physical education class injuries was available on individual pupil health records. The same injury classification was used in these records as was used in the accident reports. To estimate the number of injuries that were not recorded on official accident reports, health records of all 12th-grader pupils in 1976-1977 school year were examined for notations of physical education class-related injuries. If an injury was noted on both an accident report and on the pupil's health record, it was treated only as an official accident report injury in this study.

RESULTS

Rate and Type of Accident Report Injuries

Between September 1976 and June 1978, there were official school accident reports of 134 injuries related to participation in physical education classes. These injuries occurred during 3,737 pupil years of observation; a rate of 3.6 reported injuries per 100 participants per year. The grade and sex of pupils, type of injury, and rate per 100

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Table 1.—Injuries in Physical Education Class Noted on School Accident Reports

Grade/ Sex	No. of Pupil Years*	Sprain	Fracture	Contusion or Abrasion	Laceration	Miscellaneous	Injuries per 100 Pupil Years
9/F	435	9	1	11	0	0	4.8
M	457	3	0	3	0	0	1.3
10/F	504	11	0	6	0	1	3.6
M	440	7	1	3	2	0	3.0
11/F	495	9	1	5	4	0	3.8
M	465	16	0	4	0	0	4.3
12/F	482	5	0	8	0	0	2.7
M	459	11	1	10	1	1	5.2
Total/F	**1,916**	**34**	**2**	**30**	**4**	**1**	**3.7**
M	**1,821•**	**37**	**2**	**20**	**3**	**1**	**3.5**

*Pupil year indicates number of pupils times number of years observed.

Table 2.—Anatomical Location of Injuries in Physical Education Class Noted on School Accident Reports

	Boys	Girls
Ankle and/or foot	22	19
Lower extremities other than ankle or foot	9	7
Wrist and/or hand	10	26
Upper extremities other than wrist or hand	7	2
Trunk	1	2
Head	14	15
Total	**63**	**71**

Table 3.—Type and Location of Injuries*

	Type				Location					
	Sprain	Fracture	Contusion/ Abrasion	Laceration	Ankle/ Foot	Lower Extremity	Wrist/ Hand	Upper Extremity	Trunk	Head
Girls	3	0	3	1	2	0	3	0	0	2
Boys	12	0	7	0	12	0	6	0	0	1

*As seen by the school nurse but not noted on school accident reports.

pupil years are given in Table 1.

Overall, rates of reported injuries were approximately equal for boys and girls, although ninth grade girls had almost four times the injury rate of ninth grade boys, and 12th grade boys had approximately twice the injury rate of 12th grade girls. More than half the total injuries noted in accident reports were sprains and about 37% were contusions or abrasions. Fractures, lacerations, and miscellaneous injuries totaled about 10%. The proportions of the various injury categories were similar in both sexes and in all grades. Thirty (22%) of the 134 accident report injuries were referred for medical evaluation and 25 of the 30 (83%) received a roentgenogram to determine presence of a bone fracture. The anatomical locations of accident report injuries are given in Table 2.

Circumstances of Accident Report Injuries

Of the 134 accident report injuries, 97 were individual injuries and 37 occurred in an interaction with another participant. Of the 97 individual injuries, 33 occurred by contact with a ball, two by the pupil running into a volleyball post, one by the pupil hitting himself on the head with a bat, and the remaining 61 involved no specific contact with equipment.

Of 71 sprains, 34 (48%) occurred to the ankle and 17 (24%) to the wrist or fingers. Sixteen sprains (23%) occurred when the pupil was trying to catch or hit a ball (eg, basketball, volleyball, dodgeball), whereas 43 (61%) involved only the injured person (eg, falling). The largest single cause of contusion and abrasion in girls (14 of 30) was being struck by a field hockey stick. Of the four fractures, the two of the foot or ankle were caused by twisting the foot or ankle while in motion, and the two of the fingers were caused by contact with a basketball and by being hit with a field hockey stick.

Basketball was the activity most commonly associated with reported injuries of the ankle or foot (12 of 41). Eleven of these 12 basketball injuries occurred by twisting an ankle when coming down from a rebound. Almost half of the injuries to the wrist and hand were due to contact with a ball and occurred more frequently to girls (26 of 36) than to boys (ten of 36). Eleven of the 29 injuries to the head were caused by a ball, nine by a collision, and five by a field hockey stick.

Characteristics of Health Room Record Reported Injuries

Of the 484 members of the 1976-1977 12th-grade class sampled for injuries noted in the nurse's health room record but for which no accident report was filed, 26 (seven girls and 19 boys) were found to have sustained an injury in physical education class: a rate of 5.4 per 100 pupil years. Table 3 gives type and anatomical location of these injuries.

COMMENT

Three aspects of the physical education class-related injuries observed in this study merit comment: (1) their severity and frequency compared with injuries reported in other studies; (2) the different injury rates of boys and girls; and (3) the likelihood that these injuries could be prevented.

Comparison With Other Studies

The National Center for Education Statistics, based on a survey of 2,500 public and private secondary schools in academic year 1975-1976, reported 90,651 injuries in 4.74 million girls and 138,616 injuries in 4.93 million boys who participated in physical education classes.[2] Although these injuries were not classified by severity, type, or

location, the overall rate of 2.4 injuries per 100 pupil years is similar to that observed in the official accident report injuries in the study reported here (3.6 injuries per 100 pupil years).

This injury rate determined for physical education classes is considerably less than the injury rate determined by Garrick and Requa for competitive interscholastic athletic competitions with practices.[5] They reported two years' experience with interschool sport-related injuries in four Seattle area high schools, and found that 39 per 100 sports participants per year sustained a "medical problem resulting from athletic participation necessitating removal from a practice or competitive event and/or resulting in missing a subsequent practice or competitive event." Although the Pittsburgh pupils with official accident reports were removed from physical education participation until their injury was evaluated, the Pittsburgh and Seattle criteria for injury were not identical. However, the accident report injuries of the Pittsburgh study seem to be of similar severity to those reported in interschool sports in the Seattle study. Forty-two percent of the Seattle and 22% of the Pittsburgh study students were referred for further evaluation and care, and of those referred, 71% of the Seattle and 83% of the Pittsburgh students received roentgenograms. The Pittsburgh and Seattle injury frequency rates (3.6 per 100 physical education class participants per year and 39 per 100 sports participants per year) are not strictly comparable because of differences in hours and intensity of exposure of pupils in physical education classes and in interschool sports. Injury rates of pupils in the Pittsburgh study were calculated on the basis of a maximum of 48 hours per year spent in a variety of physical education class activities. Seattle pupil rates were calculated with respect to participation in specific sports. It is quite certain that the hours of practice and competition spent in any single sport exceeded the annual total time in physical education class (48 hours). Thus, although the Pittsburgh injury rate of 3.6 per 100 physical education class participants per year was less than a tenth of the Seattle sports injury rate calculated on a per season basis, the Pittsburgh and Seattle injury rates might have been closer if both had been based on hours of exposure in individual activities. Other factors, such as intensity of activity and complaint threshold, though difficult to assess, also would affect comparisons of injury rates in the two studies.

The injuries in the Pittsburgh study that were noted only in the nurse's health room record, seem to have been much less severe than those reported in the Seattle and National Center studies. None of these 5.4 injuries per 100 pupils per year was referred for further evaluation or care, and there were no fractures.

Rates in Girls and Boys

In the Pittsburgh study of official accident reports, there was surprisingly little difference when all high school grades were totaled between boys and girls in the frequency and apparent severity of injuries sustained in physical education class activities. Although this observation is in agreement with other reports in which boys and girls have similar injury rates in noncontact sports,[2,6] it does not necessarily follow that injury rates and severity are similar in the two sexes. There was considerable difference in official accident reports between injury rates of boys and girls in the ninth and 12th grades: girls having higher rates in the former and boys in the latter. In nurse's reports of reasons for health room visits of 12th graders, boys also outnumbered girls for physical education-related injuries. A further difficulty in comparing injury rates of boys and girls was noted by Garrick and Requa,[4] who observed that there are differences in boys' and girls' physical activities, even in those with the same names (eg, gymnastics), as well as differences between sexes in sports expertise and possibly in thresholds of tolerance to discomfort.

Prevention

Although the incidence of physical education class-related injuries in the Pittsburgh study was small and their severity mild, the possibility of prevention was considered. Most commonly, the injuries were sustained by falling or tripping, and next most commonly by contact with a ball. Both of these circumstances reflect musculoskeletal skill, conditioning, and experience. Theoretically, body conditioning and skill enhancement might reduce such injuries. It is possible, however, that the low incidence and severity of the injuries sustained in physical education classes might not provide sufficient motivation for the students involved to participate in conditioning programs to reduce such injuries. With the exception of field hockey, where protective equipment for the hands and face would possibly aid in lowering the specific injury rate, no specific set of circumstances was identified that was implicated in more than a few injuries and that was modifiable by protective equipment.

Adolescents participating in physical activity such as that required by high school physical education programs are always at risk for injury. The low incidence and mild severity of physical education class related injuries suggest that they were not a major health problem in the high school that was studied.

Lewis Nettrour, MD, suggested the study reported here.

References

1. Cahill BR, Griffith EH: Effect of preseason conditioning on the incidence and severity of high school football knee injuries. *Am J Sports Med* 6:180-183, 1978.

2. Calvert R: Athletic injuries and deaths in secondary schools and colleges, 1975-76. National Center for Education Statistics, Department of Health Education and Welfare, 1979.

3. Chambers, RB: Orthopedic injuries in athletes (age 6 to 17): Comparison of injuries occurring in six sports. *Am J Sports Med* 7:195-197, 1979.

4. Garrick JG, Requa RK: Girls' sports injuries in high school athletics. *JAMA* 239:2245-2248, 1978.

5. Garrick JR, Requa RK: Injuries in high school sports. *Pediatrics* 61:465-469, 1978.

6. Haycock CE, Gillette JV: Susceptibility of female athletes to injury. *JAMA* 236:165-167, 1976.

7. Mand C: Sports injuries and athletic conditioning. *NASSP Bulletin*, May 1978.

8. McCluskey GM, Blackburn TA, Lewis T: Prevention of ankle sprains. *Am J Sports Med* 4:151-157, 1976.

9. Mueller FO, Blyth CS: North Carolina high school football injury study: Equipment and prevention. *Am J Sports Med* 2:1-10, 1974.

Inhibition of Iron Absorption From Human Milk by Baby Food

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• We measured the effect of a common baby food, strained pears, on the absorption of iron from human milk. Five adult subjects were initially fed 1 dL of human milk that contained added ferrous citrate Fe 59; the same subjects were later fed human milk and one jar of baby food. Incorporation of ^{59}Fe into RBCs averaged approximately one quarter of the administered iron from the human milk. When the milk was combined with the baby food, incorporation was significantly decreased. The addition of a supplemental food to the diet of the breast-fed infant impairs the bioavailability of the iron from human milk.

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Infants absorb 50% to 70% of the iron present in human milk as contrasted with 10% of the iron in cow's milk and 3% to 5% of the iron in iron-fortified proprietary formulas.[1-4] Infants who are exclusively breast fed for periods of six to nine months maintain normal hemoglobin values and normal iron stores. As early as 1928, Mackay[5] reported that infants who were exclusively breast fed had higher hemoglobin values than artificially fed infants but that this difference began to disappear when the breast-fed infants were offered solid foods. More recent studies have suggested that the preferential iron balance observed in exclusively breast-fed infants is no longer present when these infants receive traditional baby foods.[6,7]

See also p 453.

These observations suggest that the superior bioavailability of iron from human milk is compromised by the presence of other foods in the diet. We report our findings that show a marked inhibition of radioiron absorption from human milk when a typical baby food is added to the test meal fed to normal adults.

SUBJECTS AND METHODS

Human milk was obtained from four lactating women who were breast feeding their infants for periods of three to six months. The human milk was pooled and stored at −20 °C until use.

Five healthy, iron-sufficient men served as subjects. After fasting for eight hours, each subject was fed 1 dL of human milk in the first test period and 1 dL of human milk and one jar (128 g) of strained pears in the second test period. After each feeding, the subjects fasted for an additional four hours.

The interval between the first and second test meal was two weeks. Ten microcuries of ferrous citrate Fe 59 (^{59}Fe) was added to the milk prior to ingestion, and iron absorption studies were performed as previously described.[1] A standard solution of the milk was prepared for analysis by diluting 1 mL of milk with 99 mL of saline.

Fourteen days after the ingestion of the first test meal, blood samples were obtained from each subject just prior to the ingestion of the second test meal and again 14 days after the ingestion of the second test meal. Red blood cell and plasma radioactivity were assessed from duplicate 2.5-mL samples.

The blood volume of each subject was estimated by applying each subject's weight and height to well-established nomograms.[8] The RBC mass was determined by multiplying the hematocrit value of each subject by the blood volume. No correction was made for trapped plasma. The total ^{59}Fe incorporated into RBCs after ingestion of each test meal was determined by the following formula:

RBC volume × (counts per minute [cpm]/mL of RBC) = total cpm incorporated.

The quantity of iron incorporated into RBCs was then calculated by the following method:

μg of elemental iron incorporated = total cpm incorporated × (μg of elemental iron ingested/cpm of ^{59}Fe ingested).

The percentage of ingested ^{59}Fe incorporated from human milk with and without the pears was then compared by the paired Student's t test.

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Erythrocyte Incorporation of Ferrous Citrate Fe 59				
	Iron Incorporated, %		Iron Incorporated, μg	
	From Human Milk	From Human Milk With Pears	From Human Milk	From Human Milk With Pears
Subjects				
1	16.1	5.9	0.012	0.008
2	31.4	9.0	0.024	0.012
3	10.3	3.4	0.007	0.005
4	26.3	3.5	0.020	0.005
5	34.3	6.7	0.026	0.009
Mean ± SD	23.68 ± 10.20	5.70 ± 2.35	0.0178 ± 0.007	0.0078 ± 0.002
P value	< .01		< .01	

RESULTS

The mean RBC incorporation of ^{59}Fe from human milk was 23.7% of the administered dose in the first feeding as contrasted with only 5.7% in the second feeding, which included both human milk and strained pears (Table). In all five subjects, an inhibition of iron incorporation was observed when they were fed pears; the mean inhibition was 76% (range, 64% to 87%).

The iron content of the human milk used in this study was 0.76 mg/L. The iron content of the pears was 0.06 mg per jar. According to these figures, the subjects incorporated an average of 0.0178 mg of iron from the first meal as compared with an average of 0.0078 mg of iron from the second meal.

COMMENT

Layrisse and co-workers[9] have demonstrated that exogenous iron added to ingested food is absorbed at the same rate as the endogenous iron in the food. Taking advantage of this observation, we have previously shown that approximately 20% of the radioiron added to a test meal of human milk is incorporated into the erythrocytes of normal adults.[1,2] The findings in this study are in agreement with those previously reported. The iron incorporated into erythrocytes is estimated to be only 80% of the actual iron absorbed in a test feeding.[8] Infants normally absorb two to five times as much iron from a given food source as do normal adults.[4,10] Saarinen and associates[3] used the method of counting total-body iron after the administration of a tracer dose of iron and found that normal, term infants of approximately 6 months of age absorbed 49% of the iron in human milk. The factor or factors in human milk that are responsible for this enhanced iron absorption are presently unknown.[2] This enhanced bioavailability does not appear to be a consequence of the presence of lactoferrin in human milk.

Saarinen and Siimes[6] estimated the changes in total-body iron content during the growth of infants fed three different milk regimens. The total-body iron was calculated as the sum of the hemoglobin iron and the body-storage iron as reflected by the serum ferritin concentration. The calculated percentage absorption of iron in infants who were exclusively breast fed was estimated to be 70%. After 4 months of age, when solid foods were introduced into the diet of the breast-fed infants, the monthly increments in total-body iron became much smaller. The authors hypothesized that fruits and vegetables produced an inhibitory effect on the absorption of iron from human milk, and they recommended that the introduction of vegetables and fruits be delayed in infants who are being breast fed.

Pears were selected for our study because they are commonly recommended as one member of the fruit group to be used to initiate the feeding of solid foods. Despite the fact that a jar of pears contains 11 mg of ascorbic acid, a facilitator of iron absorption, the pears inhibited iron absorption. The basis for this inhibition is unknown.

The finding that one commonly used infant food markedly inhibits iron absorption from human milk may help to explain why some investigators have failed to demonstrate a superior nutritional state for iron in breast-fed infants.[7] In most comparisons, the breast-fed infants were also being fed solid foods by 3 to 6 months of age.

Pat Viele and the Syracuse, NY, La Leche League helped in this study. Susan Rathbun provided technical assistance.

References

1. McMillan JA, Landaw SA, Oski FA: Iron sufficiency in breast-fed infants and the availability of iron from human milk. *Pediatrics* 58:686-691, 1976.

2. McMillan JA, Oski FA, Lourie G, et al: Iron absorption from human milk, simulated human milk, and proprietary formulas. *Pediatrics* 60:896-900, 1977.

3. Saarinen UM, Siimes MA, Dallman PR: Iron absorption in infants: High bioavailability of iron is indicated by the extrinsic-tag method of iron absorption and by the concentration of serum ferritin. *J Pediatr* 91:36-39, 1977.

4. Schulz J, Smith NJ: A quantitative study of the absorption of food iron in infants and children. *Am J Dis Child* 95:109-119, 1958.

5. Mackay HMM: Anemia in infancy: Its prevalency and prevention. *Arch Dis Child* 3:1175-1191, 1928.

6. Saarinen UM, Siimes MA: Iron absorption from breast milk, cow's milk, and iron-supplemented formula: An opportunistic use of changes in total-body iron determined by hemoglobin, ferritin, and body weight in 132 infants. *Pediatr Res* 13:143-147, 1979.

7. Woodruff CW, Latham C, McDavid S: Iron nutrition in the breast-fed infant. *J Pediatr* 90:36-38, 1977.

8. Hosain F, Marsaglia G, Finch CA: Blood ferrokinetics in normal man. *J Clin Invest* 46:1-12, 1967.

9. Layrisse M, Martinez-Tores C, Cook JD, et al: Iron fortification of food: Its measurement by the extrinsic-tag method. *Blood* 41:333-352, 1973.

10. Kimber C, Weintraub LR: Malabsorption of iron secondary to iron deficiency. *N Engl J Med* 279:453-459, 1968.

Salicylate Therapy in Juvenile Rheumatoid Arthritis

Dose, Serum Level, and Toxicity

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• In a prospective study of aspirin therapy for 67 children with juvenile rheumatoid arthritis, we have found that (1) doses greater than 100 mg/kg/day of aspirin may be necessary to achieve therapeutic salicylate levels greater than 20 mg/dL; (2) no improvement in clinical remission rate is seen at salicylate levels greater than 30 mg/dL; (3) clinical toxicity to aspirin is of relatively low incidence (16%), and infrequently causes serious morbidity; (4) symptomatic SGOT elevations are common in the first three months after onset of therapy; and (5) these elevated SGOT levels generally return to normal despite continuation of therapy.

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Recent publicity about potential toxic effects of aspirin has caused great concern among many parents of patients receiving long-term aspirin therapy for juvenile rheumatoid arthritis (JRA). There is also controversy among pediatric rheumatologists about the risks of using high doses (>100 mg/kg/day) of aspirin[1-3] and concern about the incidence of aspirin-induced hepatotoxic effects.[3-5]

These concerns have resulted in many children with JRA being either started on, or switched to, a regimen of newer nonsteroidal anti-inflammatory drugs before an adequate trial of aspirin therapy has been undertaken. Many of these new drugs have not yet been adequately tested in children, and their efficacy and incidence of side effects are not known. Furthermore, most of these drugs are considerably more expensive than aspirin. To better define the therapeutic dosage and toxic effects of aspirin, we undertook a prospective study of patients with JRA in the Pediatric Rheumatology Clinic of the Children's Hospital of Philadelphia.

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The study was designed to answer several questions: (1) What is the dosage of aspirin necessary to obtain a clinical response? (2) What is the incidence of clinical toxic reactions? (3) How do serum salicylate levels correlate with the dosage of aspirin, the clinical response, and evidence of clinical or biochemical toxicity? Patients qualified for the study if they met the preliminary criteria for JRA as defined by the JRA Criteria Subcommittee of the Arthritis and Rheumatism Association.[6]

SUBJECTS AND METHODS

Children were given aspirin in four divided doses. The total daily dosage was calculated to be 100 mg/kg/day for children who weighed up to 25 kg. For children weighing more than 25 kg, the starting dosage of aspirin was 2.4 to 3.6 g/day. Serum salicylate levels (drawn two hours after a morning dose of aspirin) were obtained seven to 14 days after start of therapy. The aspirin dosage was increased gradually or decreased as necessary in attempts to obtain salicylate levels between 20 and 30 mg/dL. In patients with poor clinical responses to aspirin, the dosage was increased to obtain levels as great as 35 mg/dL. A rheumatology nurse-practitioner carefully explained the administration of aspirin and symptoms of toxicity to each patient and the patient's parents.

Frequent home telephone contact was made to promote compliance and closely monitor toxic reactions. After stabilization, salicylate levels were followed up routinely every three months. The SGOT levels were obtained simultaneously with salicylate levels since they have been shown to be sensitive indicators of aspirin-induced hepatotoxic effects.[7]

A complete standardized history and physical examination were obtained for the patient at each visit to judge clinical response to the aspirin. All patients were examined by one of two staff pediatric rheumatologists. Global assessment of clinical responses was graded in three categories: (1) remission, which was the absence of clinical evidence of active joint disease; (2) partial response, which represented those patients demonstrating improvements from their previous examinations; and (3) no response, which consisted of those patients who showed no change in their assessments or worsening of their conditions. Global assessments were based on the following criteria: duration of morning stiffness, functional level, parent-patient self-assessment, and an articular index.

Total serum salicylate levels were measured by the quantitative colorimetric assay of Trinder.[8] The SGOT values were determined by standard laboratory procedure. Normal SGOT values in our laboratory are in the range of 0 to 40 IU. Statistical analyses of data were performed using χ^2 analysis with the Yates correction and the Student's t test.[9]

RESULTS

Our patient population consisted of 67 patients followed up for a mean period of 14.7 months. Children ranged in age from 10 months to 18 years. Of these patients, 17 (25%) had the systemic-type of JRA; 17 (25%) had the polyarticular-type; and 33 (50%) had the pauciarticular-type. Thus, our study population had a slight excess of patients with pauciarticular disease.[10,11]

The average serum salicylate level of each patient during the period of study was calculated and correlated

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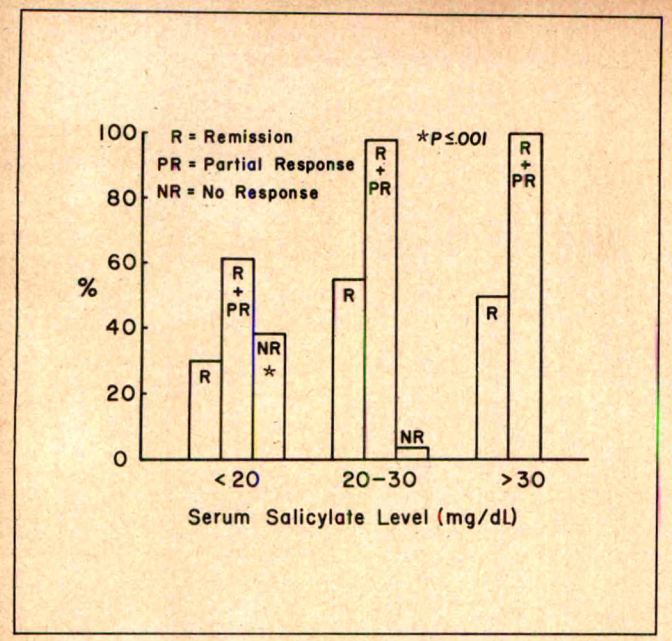

Fig 1.—Clinical response vs serum salicylate level in patients with juvenile rheumatoid arthritis. Number of patients (N) in each serum level group: < 20 mg/dL, N = 13; 20 to 30 mg/dL, N = 48; > 30 mg/dL, N = 6.

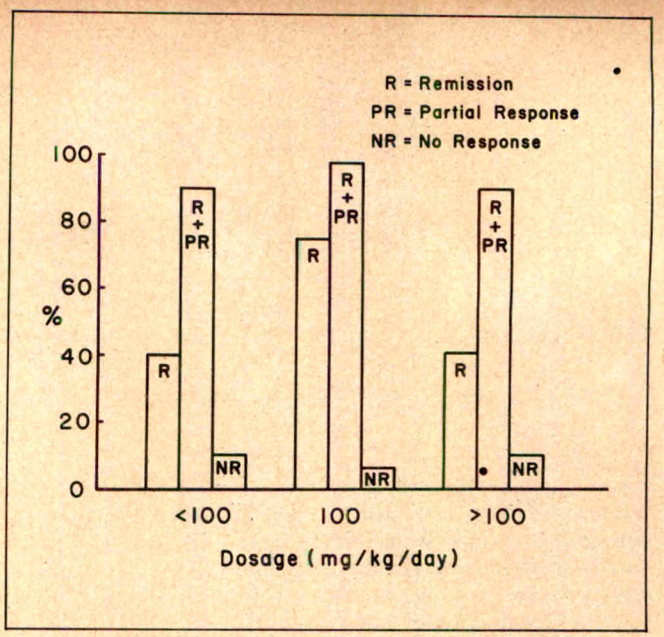

Fig 2.—Clinical response vs aspirin dosage in patients with juvenile rheumatoid arthritis. Number of patients (N) in each aspirin dosage group: < 100 mg/kg/day, N = 31; 100 mg/kg/day, N = 18; > 100 mg/kg/day, N = 18.

Aspirin Toxicity in Juvenile Rheumatoid Arthritis
Reasons for discontinuation
Abdominal pain, 4
Symptomatic hepatitis, 5
Skin rash, 2
11 patients for whom aspirin therapy was stopped
Polyarticular, 5
Systemic, 5
Pauciarticular, 1

with clinical response. Twelve patients whose salicylate levels varied widely (> 15 mg/dL) because of poor compliance or perhaps other factors such as altered disposition (absorption, metabolism, or excretion) of aspirin were excluded from the study. In most cases (45/67, or > 70%), salicylate levels for individual patients varied by < 10 mg/dL for any given aspirin dosage. The global assessment of patient responses compared with average serum salicylate levels is shown in Fig 1. It shows a significantly improved response for those patients with salicylate levels greater than 20 mg/dL ($P < .001$). The rate of response was no better for patients with levels greater than 30 mg/dL.

Comparison of global assessment of response with aspirin dosage is shown in Fig 2. There was no significant difference in response rates relative to the aspirin dosage used. Sixteen of our 56 patients who tolerated aspirin therapy (ie, aspirin use was discontinued for 11 patients) were treated with dosages greater than 100 mg/kg/day to obtain therapeutic salicylate levels. Thus, in almost 30% of our patients, dosages in excess of 100 mg/kg/day were required to maintain salicylate levels greater than 20 mg/dL.

Eleven of the children had toxic reactions requiring withdrawal of aspirin therapy. The nature of the toxic reactions and the clinical subgroups of JRA of these children is given in the Table.

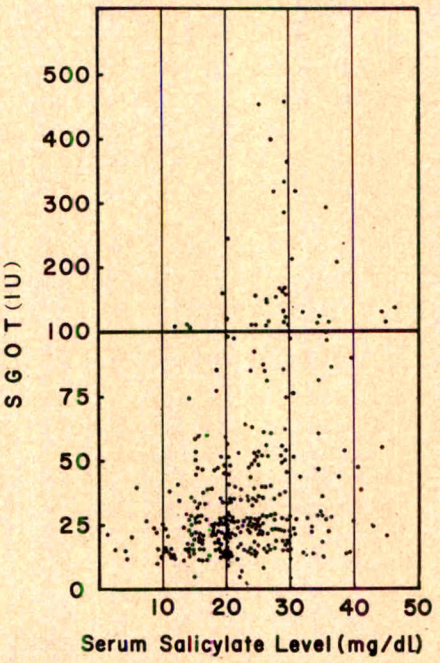

Fig 3.—The SGOT vs serum salicylate levels for juvenile rheumatoid arthritis.

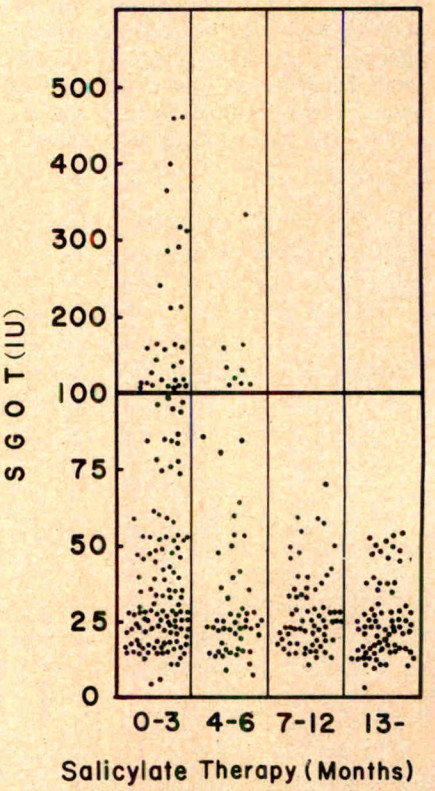

Fig 4.—The SGOT elevation vs duration of aspirin therapy for juvenile rheumatoid arthritis.

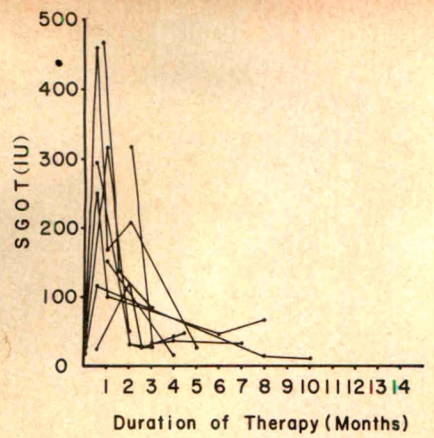

Fig 5.—Serial SGOT elevations for nine newly diagnosed cases of juvenile rheumatoid arthritis treated with aspirin.

Hepatotoxic effects, manifested by modest SGOT elevations (< 400 IU), were frequently seen within one month after the start of therapy. However, most of these patients showed no clinical evidence of hepatitis; occasionally they would complain of nonspecific abdominal pain without other evidence of hepatitis from results of either history or physical examination. In most of these patients (15 of 18), SGOT values returned to normal in the initial three months of therapy. To further investigate these aspirin-induced hepatotoxic effects, serum salicylate levels were compared with simultaneous SGOT determinations for 93 patients (our original group of 56, plus 37 patients whose conditions were diagnosed after discontinuation of the study). Figure 3 is a scattergram of 340 simultaneous salicylate levels and SGOT determinations in these 93 patients. As previously demonstrated by others, it shows that, in patients with JRA, there is a positive correlation between the salicylate level and the SGOT elevation.[4,7,12]

Figure 4 shows SGOT values correlated with duration of therapy for 93 patients. Substantial decreases in the SGOT values within the first three months of therapy are noted. Those five patients with symptomatic hepatitis for whom aspirin therapy was discontinued are excluded from this graph. In Fig 5, serial SGOT values are shown for nine patients in whom salicylate levels were within the therapeutic range. This shows a similar pattern of decrease in SGOT values over time.

COMMENT

Our study showed that serum salicylate levels greater than 20 mg/dL correlated well with improved clinical response. Although this serum level is frequently used as a therapeutic level,[3] its efficacy is not well documented in the literature. No substantial improvement in clinical response was seen at salicylate levels greater than 30 mg/dL. Our subjective opinion that certain patients seem to do better at salicylate levels greater than 30 mg/dL was not demonstrated in this study; however, this possibility may be masked by the fact that some patients in the "greater than 30 mg/dL" group who are in the remission or partial-responder groups may have had their aspirin dosages increased because of partial or poor responses at lower salicylate levels. Thus, there may be a subgroup that requires higher salicylate levels for good clinical response.

Sixteen patients (28%) required aspirin dosages in excess of 100 mg/kg/day to obtain consistent salicylate levels greater than 20 mg/dL. There was no increased incidence of clinical toxic effects seen in these patients. The concern expressed by other authors about clinical toxic reactions resulting from use of aspirin dosages greater than 100 mg/kg/day[1] was not supported by our study.

In contrast to the opinions of others,[7-13] our study did not demonstrate that aspirin toxicity was more frequent in patients with the systemic form of JRA than in those with the polyarticular form. However, there were significantly fewer patients with pauciarticular disease in whom it was necessary to discontinue aspirin therapy because of hepatotoxic effects ($P < .025$).

Patients with symptomatic hepatotoxic effects had vomiting, liver tenderness, and hepatomegaly. All showed marked elevations in SGOT levels (frequently > 1,000 IU), and some had prolongation of the prothrombin time.

It is interesting that five of the 11 patients with symptoms of aspirin toxicity were subsequently given salicylate choline as alternative therapy and successfully treated (obtaining serum salicylate levels in the therapeutic range of 20 to 30 mg/dL) without recurrence of toxic symptoms. Thus, to summarize the clinical toxic data, aspirin was relatively well tolerated in our patients and there were no serious toxic effects such as overt gastrointestinal hemorrhage or peptic ulcer. Therapy with the drug was discontinued in 16% of our patients. Ninety-one percent of the group tolerated either aspirin or salicylate choline as the sole anti-inflammatory agent.

CONCLUSION

We believe this study supports the contention that aspirin, even in high doses, remains a safe and effective agent for treatment of JRA. Because of its effectiveness, low incidence of toxic effects, and low cost, an adequate trial of aspirin should generally be attempted before resorting to other nonsteroidal anti-inflammatory drugs.

Nonproprietary Name and Trademark of Drug

Salicylate choline—*Arthropan.*

References

1. Makela A, Yrjana T, Haapasaari J: Dosage of salicylates with juvenile rheumatoid arthritis. *Scand J Rheumatol* 4:250-252, 1975.
2. Calabro JJ, Burnstein SL, Staley HL: Letter to the editor. *Scand J Rheumatol* 5:251-252, 1976.
3. Schaller JG: Chronic salicylate administration in juvenile rheumatoid arthritis: Aspirin 'hepatitis' and its clinical significance. *Pediatrics* 62(suppl):916-925, 1978.
4. Russell AS, Sturge RA, Smith MA: Serum transaminases during salicylate therapy. *Br Med J* 2:428-429, 1971.
5. Levy G, Yaffe SJ: Clinical implications of salicylate-induced liver damage. *Am J Dis Child* 129:1385-1386, 1975.
6. JRA Criteria Subcommittee: Criteria for classification of juvenile rheumatoid arthritis. *Bull Rheum Dis* 25:712-719, 1973.
7. Athreya BA, Moser G, Cecil HS, et al: Aspirin-induced hepatotoxicity in juvenile rheumatoid arthritis. *Arthritis Rheum* 18:347-352, 1975.
8. Trinder P: Rapid determination of salicylate in biological fluids. *Biochem J* 57:301-303, 1954.
9. Mainland D: *Elementary Medical Statistics*, ed 2. Philadelphia, WB Saunders Co, 1963, pp 224-293.
10. Schaller J, Wedgewood RJ: Juvenile rheumatoid arthritis: A review. *Pediatrics* 50:940-953, 1972.
11. Stillman JS, Barry PE: Juvenile rheumatoid arthritis: Series 2. *Arthritis Rheum* 20(suppl):171-175, 1977.
12. Rich RR, Johnson JS: Salicylate hepatotoxicity in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 16:1-9, 1973.
13. Bernstein BH, Singsen BH, King KK, et al: Aspirin-induced hepatotoxicity and its effect on juvenile rheumatoid arthritis. *Am J Dis Child* 131:659-663, 1977.

Coarctation of the Aorta in Children

Late Results After Surgery

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• From 1960 to 1970, 110 patients underwent operation for coarctation of the aorta. The overall mortality was 23%. However, in infants operated on at less than 6 months of age, the mortality was 63%, whereas there was only a 4% mortality in those operated on after 6 months of age. Late follow-up was available in 87 patients from five to 15 years postoperatively. There was a 14% frequency of recoarctation in the group of long-term survivors. Systemic hypertension, defined as an upper extremity blood pressure greater than 140/90 mm Hg, was found in 23% of the survivors. This study has demonstrated a significant frequency of postcoarctectomy hypertension and residual hemodynamic and angiographic abnormalities in patients without clinical evidence of recoarctation. This indicates the need for continued long-term follow-up of these patients.

(*Am J Dis Child* 134:464-466, 1980)

Successful surgical correction of coarctation of the aorta (COA) has been carried out since 1939. Several studies evaluating the long-term results after operation have demonstrated substantial residual cardiovascular abnormalities.[1-3] These residua include persistent or recurrent stenosis of the original coarctation, hypertension, and premature cardiovascular death. The etiology of the persistent hypertension is uncertain as it can be related to recoarctation in less than approximately one third of the cases.[2] This report reviews the immediate and long-term results of surgery in a series of patients who underwent operation for COA at Children's Hospital of Pittsburgh.

SUBJECTS AND METHODS

In the period from 1960 to 1970, 110 patients underwent surgical correction of COA, present either as an isolated defect or associated with a patent ductus arteriosus or a ventricular septal defect (VSD). However, patients with aortic or mitral valve abnormalities were included if these lesions did not influence the initial management of their conditions. Patients with COA associated with complex congenital heart disease such as conotruncal abnormalities or valvular atresias were not included. All inpatient and outpatient records were reviewed, as were data from postsurgical cardiac catheterizations when available. Patients were grouped according to age at operation, and the immediate and late results of surgery were tabulated.

Late follow-up was available for 87 patients from five to 15 years postoperatively. Cardiac catheterization was performed on 22 long-term survivors because of either clinical evidence of recoarctation (12 patients) or associated cardiac anomalies (ten patients). These 22 patients were also grouped according to age at operation, and the results concerning the frequency of hypertension and recoarctation as well as angiographic and hemodynamic data were analyzed.

Significant hypertension was arbitrarily defined as blood pressure (BP) of greater than 140/90 mm Hg obtained in the sitting position on repeated determinations. Patients were considered to have the clinical findings of recoarctation when they had a systolic BP differential between the upper and lower extremities that was greater than 20 mm Hg. As this study was retrospective, we chose to use these rigid criteria for significant hypertension and recoarctation so that patients with borderline values would not falsely increase the frequency. The term recoarctation has been used in this study since it is impossible to determine whether a postoperative BP gradient is due to residual or recurrent coarctation.

RESULTS

Of the 110 patients included in this study, the overall mortality was 23%. Of the 25 deaths, 19 occurred within one month of the operation and were considered early deaths. There was a striking relationship between mortality and age at operation (Table 1). Of the 35 patients, 22 (63%) who underwent surgery at less than 6 months of age died, whereas the mortality for those more than 6 months of age was

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Table 1.—Coarctation of the Aorta, 1960 to 1970

Age at Operation	No. of Patients	Mortality*		
		Early	Late	Total
< 6 mo	35	18	4	**22** (63)
6 mo-2 yr	5	...	1	**1** (20)
2-5 yr	11	1	...	**1** (9)
6-8 yr	14	...	1	**1** (7)
9-12 yr	29	...	...	**0**
> 12 yr	16	...	...	**0**
Total	**110**	**19** (17)	**6** (6)	**25** (23)

*Early is less than one month after operation; late, greater than one month after operation. Numbers in parentheses indicate percentages.

Table 2.—Recoarctation in Long-term Survivors After Coarctectomy

Age at Operation	No. of Patients	Recoarctation of Aorta,* No. (%)
< 6 mo	14	6 (43)
6 mo-1 yr	4	0
2-5 yr	10	2 (20)
6-8 yr	14	2 (14)
9-12 yr	29	2 (7)
> 12 yr	16	0
Total	**87**	**12** (14)

*Systolic gradient is greater than 20 mm Hg (documented by catheterization). Reoperation performed for two in greater than 6-month-old group, one in 2-5-year-old group.

Table 3.—Hypertension in Long-term Survivors

Age at Operation	No. of Patients	Hypertensive		Normotensive	
		Total No. (%)	Recoarctation of Aorta*	Total No. (%)	Recoarctation of Aorta*
< 6 mo	14	2 (14)	2	12 (86)	4
6 mo-1 yr	4	...	...	4 (100)	...
2-5 yr	10	2 (20)	2†	8 (80)	...
6-8 yr	14	1 (7)	...	13 (93)	2
9-11 yr	29	8 (28)	2	21 (72)	...
> 12 yr	16	7 (44)	1	9 (56)	...
Total	**87**	**20** (23)	**7**	**67** (77)	**6**

*Systolic gradient is greater than 20 mm Hg.
†One patient has renal disease as well.

4%. All but one of the early deaths occurred in children less than 6 months of age who frequently had associated intracardiac lesions such as a VSD. There were six late deaths (ie, those occurring more than one month postoperatively). Three died in infancy from congestive heart failure with or without superimposed pneumonia, and a fourth infant died during operation for mitral stenosis. One child died during operation for a VSD and another child died of subacute bacterial endocarditis on a mildly stenotic bicuspid valve.

Twelve of the 87 patients (14%) with long-term follow-up, from five to 15 years postoperatively, had clinical evidence of recoarctation. In each case, cardiac catheterization demonstrated a systolic gradient (<20 mm Hg) across the coarcted segment. The relationship between the frequency of recoarctation and age at operation is given in Table 2. Although only 32% of all the patients studied were less than 6 months of age at the time of operation, 50% (six of 12) of those who had recoarctation develop were in this age category.

Systemic hypertension was found in 20 of the 87 (23%) long-term survivors. The relationship between hypertension, recoarctation, and age at operation is depicted in Table 3. Seven of the 20 hypertensive patients had recoarctation to explain their elevated BP (one of these also had renal disease). The frequency of persistent hypertension increased with the age at operation. Four of 28 patients (14%) younger than 6 years of age at operation had persistent hypertension, whereas 16 of 59 patients (27%) older than 6 years of age at operation had hypertension at follow-up. Of note is the fact that all four of those in the younger age group had recoarctation as an explanation for their hypertension, whereas only three of 16 (19%) of the hypertensive older children had residual aortic narrowing. The frequency of postoperative hypertension for patients in the older age group at the time of operation was unrelated to the duration of follow-up.

Cardiac catheterization data for 22 of the long-term survivors were analyzed. Twelve of these patients were catheterized because of clinical evidence of recoarctation and all 12 were found to have residual systolic gradients greater than 20 mm Hg. Of these 12 patients, six were hypertensive (BP >140/90 mm Hg).

Of the ten patients not considered to have recoarctation clinically, seven had persistent systolic gradients (three <10 mm Hg, four from 10 to 20 mm Hg) and angiographic evidence of some narrowing at the site of the previous coarctation repair. The other three patients had no systolic gradient. None of these ten patients showed signs of hypertension.

COMMENT

The overall mortality in this series was 23%, and this was definitely related to surgery performed on infants less than 6 months of age, often with associated intracardiac lesions (early mortality in this age group was 50%). In the last five years, with improvements in operative techniques, postoperative care, and the trend toward early operation on sick infants, the mortality in this age group in our institution has been reduced to less than 20% and occurs mainly in infants less than 1 month of age. The majority of these sick infants have an associated VSD. This combination of pressure and volume overload leads to the early appearance of congestive heart failure. The conditions of these infants have been successfully managed by coarctectomy alone, at our institution.[4] In most instances, the VSD does not necessitate any additional surgical intervention in infancy.

Previous studies have demonstrated that even though there has been

almost 40 years of experience with surgical correction of coarctation of the aorta, there are important cardiovascular abnormalities at long-term postoperative follow-up. Maron et al[1] reported that there was a 12% frequency of premature cardiovascular-related deaths (ie, ruptured major arterial vessel, congestive failure, or early arteriosclerotic vascular disease) in patients after coarctectomy. The mean age of death in that series was 34 years, which, interestingly, was the average life span prior to the surgical era.[1] In addition, persistent hypertension was found in 34% of their postoperative patients. In a review by Nanton and Olley[2] of the experience at Toronto Hospital for Sick Children, 24% of patients remained hypertensive after operation. This hypertension could be related to recoarctation or some other definite cause (ie, renal disease or aortic insufficiency) in only approximately one third of the cases. In this series, there was an 11% frequency of recoarctation.

The review of our experience at Children's Hospital of Pittsburgh confirms the significant incidence of hypertension at long-term follow-up. The overall frequency was 23%; however, it was somewhat more common in children who were operated on after the age of 6 years (27% vs 14% in those <6 years of age). Although varying methodologies and lack of agreed-on criteria for defining hypertension in children and adolescents have led to considerable variation in estimates of its frequency in a normal population, recent studies have indicated a maximum frequency of hypertension between 2.5% and 12.2% in this age group.[5] Therefore, it is clear that hypertension is found much more often in patients who have had coarctectomy than in the general population.

Recoarctation occurred in an overall frequency of 12%, but it was much more common in those operated on during the first 6 months of life. Persistent hypertension in children operated on before 6 years of age could be related to recoarctation in every case, whereas the elevated BP was largely unexplained in the older age group (only four of 16 had recoarctation). This suggests that persistent hypertension in children without clinical evidence of recoarctation may be related to prolonged preoperative hypertension and the subsequent development of structural or functional vascular changes. However, it is possible that patients operated on at younger ages may subsequently have a similar incidence of hypertension develop when followed up for longer periods of time.

Several studies have documented the increased frequency of exercise-induced hypertension in patients who have had previous operations for COA.[6,7] A recent report by Freed and co-workers[8] concluded that this abnormal response to exercise after coarctectomy may be due to mild but important recoarctation that was not predicted by the low resting gradient between upper and lower extremity BPs. This conclusion is supported by the rather high incidence of residual hemodynamic and angiographic abnormalities in patients without clinical evidence of important recoarctation found in our study.

Newer surgical techniques such as the subclavian patch procedure may reduce the incidence of recoarctation. However, more experience and longer follow-up will be necessary before the relative merits of these techniques can be evaluated.

Postoperative evaluation of patients who have had repair of COA should include careful documentation of BP in the lower extremities (as well as upper) in both the resting state and during exercise testing. In view of the substantial postoperative cardiovascular residua (especially hypertension and recoarctation) amply documented by this study and others in the literature, careful long-term follow-up of these patients as well as elimination of other cardiovascular disease risk factors is necessary.

James R. Zuberbuhler, MD, and Cora C. Lenox, MD, helped in the preparation of this manuscript. They also devoted time to the clinical care of these patients. Beverly Collins provided technical assistance.

References

1. Maron BJ, Humphries O, Rowe RD, et al: Prognosis of surgically corrected coarctation of the aorta. *Circulation* 47:119-126, 1973.
2. Nanton MA, Olley PM: Residual hypertension after coarctectomy in children. *Am J Cardiol* 37:769-772, 1976.
3. Simon AB, Zloto AE: Coarctation of the aorta: Longitudinal assessment of operated patients. *Circulation* 50:456-464, 1974.
4. Neches WH, Park SC, Lenox CC, et al: Coarctation of the aorta with ventricular septal defect. *Circulation* 55:189-194, 1977.
5. Loggie JMH, New MI, Robson AM: Hypertension in the pediatric patient: A reappraisal. *J Pediatr* 94:685-699, 1979.
6. Taylor SH, Donald KW: Circulatory studies at rest and during exercise in coarctation of the aorta before and after operation. *Br Heart J* 22:117-139, 1960.
7. James FW, Kaplan S: Systolic hypertension during submaximal exercise after correction of coarctation of the aorta. *Circulation* 50(suppl II):II-27-II-34, 1974.
8. Freed MD, Rocchini A, Rosenthal A, et al: Exercise-induced hypertension after surgical repair of coarctation of the aorta. *Am J Cardiol* 43:253-258, 1979.

Transient 'Lazy-Leukocyte' Syndrome During Infancy

Satoru Yoda, MD; Hironori Morosawa, MD; Atsushi Komiyama, MD, PhD; Taro Akabane, MD, PhD

• A male infant with transient severe neutropenia and defective neutrophilic mobility is described. He had recurrent upper respiratory infections that responded well to antibiotics. The neutrophilic counts continued to be less than 300/cu mm, and neutrophilic random mobility and chemotaxis were persistently defective during early infancy but were normal at 16 months of age. No ultrastructural abnormality was found in the neutrophils. Phagocytic and bactericidal abilities of the cells were not impaired. Bone marrow was normal. The clinical and laboratory findings suggest that this disorder is transient "lazy-leukocyte" syndrome.

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In recent years, much attention has been paid to the relationship between neutropenia and defective neutrophilic mobility in patients with recurrent pyogenic infections.[1,2] We describe a male infant in whom severe neutropenia and defective neutrophilic mobility were persistently present during early infancy and in whom their spontaneous normalization occurred at 16 months of age. To our knowledge, such a patient has as yet not been reported and the disorder seems to be transient "lazy-leukocyte" syndrome.

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REPORT OF A CASE

An 8-month-old male infant came to our clinic in October 1977 with a history of recurrent infections. He was born at term after a normal pregnancy. He was in good health until 4 months of age when he visited another hospital for tonsillitis and was first discovered to be severely neutropenic. During the next four-month period, during which he was followed up at the hospital, he had recurrent tonsillitis that responded well to antibiotics and he had persistent neutropenia (neutrophils were less than 300/cu mm). He had stomatitis twice but no pyogenic infections except tonsillitis. Family history was unremarkable.

Physical examination showed a well-developed infant. The liver was palpable 2 cm below the right costal margin. There was no enlargement of the spleen and lymph nodes. He had no eczema.

Hemoglobin concentration was 12.1 g/dL; platelet count, 178 × 10^3/cu mm; and leukocyte count, 10,200/cu mm, with 2% neutrophils, 4% eosinophils, 1% basophils, 86% lymphocytes, and 7% monocytes. Bone marrow was normocellular and showed a myeloid-erythroid ratio of 3:1. Differential cell count indicated 2.8% myeloblasts (normal range, 0.2% to 5.0%), 8.0% promyelocytes (0.5% to 10.0%), 6.6% myelocytes (5.0% to 15.0%), 7.0% metamyelocytes (5.0% to 15.0%), 17.4% band forms (5.0% to 20.0%), and 5.3% fully matured segmented neutrophils (1.0% to 15.0%). Serum immunoglobulin concentrations were as follows: IgG, 1,572 mg/dL; IgA, 48 mg/dL; IgM, 130 mg/dL; IgD, 0 mg/dL; and IgE, 7 units/mL. Serum complement levels were: C3, 128 mg/dL; and C5, 7.8 mg/dL. Circulating T (51%) and B (30%) lymphocytes were normal in number as estimated by rosette formation with sheep erythrocytes and with those coated with specific antibody and complement, respectively.

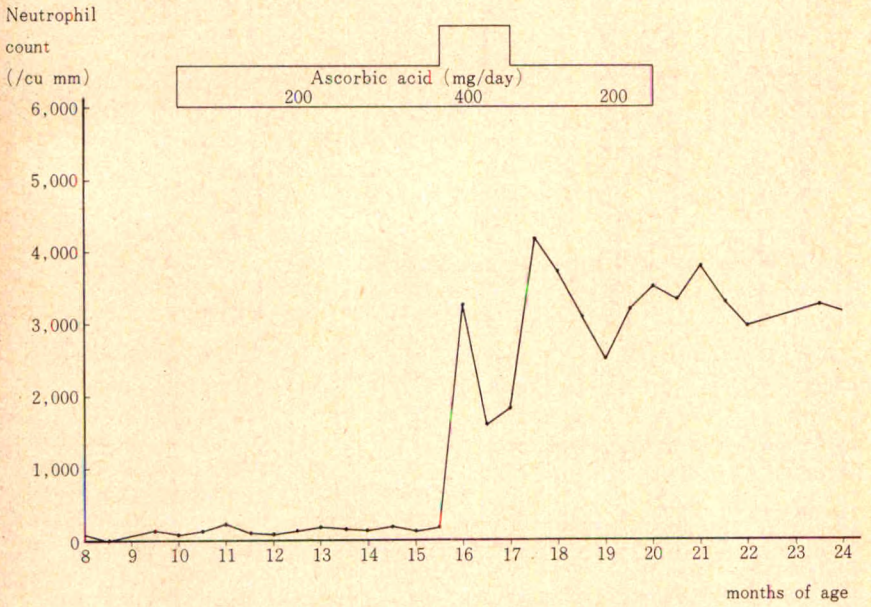
Tritiated-thymidine uptake by peripheral lymphocytes was normal after phytohemagglutinin, concanavalin A, or pokeweed-mitogen stimulation. Delayed hypersensitivity response to *Candida*, streptokinase-streptodornase, or purified protein derivative was negative, and that to phytohemagglutinin was positive.

At 10 months of age, the patient started to receive ascorbic acid therapy (200 mg daily), with no clinical and hematologic improvements. During the next five months, he experienced stomatitis, tonsillitis, or bronchitis on several occasions, and neutropenia persisted. At 15½ months of age, the dosage of ascorbic acid was increased to 400 mg daily. Two weeks later, the neutrophilic counts increased to normal range and have remained at normal levels until the latest examination, at 24 months of age, although the ascorbic acid dosage

Serial Studies of Neutrophilic Count and Mobility

Age, mo	Neutrophilic Count, Per cu mm	Neutrophilic Mobility: Random Capillary Tube*	Neutrophilic Mobility: Mobility Filter†	Neutrophilic Mobility: Chemotaxis‡
8	180	46.0	22.6	22.0
10	186	41.3	Not done	31.6
11	298	50.0	Not done	39.4
16	3,216	96.0	140.0	96.2

*Migration distance of the patient divided by migration distance of the control times 100 (%).
†Random mobility index of the patient divided by random mobility index of the control times 100 (%).
‡Chemotactic index of the patient divided by chemotactic index of the control times 100 (%).



Serial neutrophilic counts and ascorbic acid administration.

was decreased to 200 mg daily at 17 months and was discontinued at 20 months of age (Fig 1).

MATERIALS AND METHODS

All studies except peripheral neutrophilic counts were performed when the patient was free of infection. Peripheral neutrophilic counts were studied at intervals from three days to one month during the observation period. For studies of neutrophilic morphology and functions, heparinized peripheral blood was obtained from the patient and from several control patients in whom neither hematologic nor immunologic abnormalities were found. Neutrophilic suspension was prepared as previously reported.[3] Electron microscopy of neutrophils was carried out as described elsewhere.[3] In brief, neutrophils were fixed with 2.5% glutaraldehyde fixation and 1% osmium tetroxide fixation, and they were routinely processed for electron microscopy. Epinephrine hydrochloride and hydrocortisone sodium succinate stimulation tests were routinely done: epinephrine hydrochloride (1:1,000), 0.2 mL, was given intravenously, and hydrocortisone sodium succinate, 4 mg/kg, intravenously. Leukocyte migration in vivo was measured by the method of Rebuck and Crowley.[4] Random mobility was studied in vitro by the capillary tube method[5] and by the filter technique using a membrane filter, 8 μ in pore size, and a Boyden chamber. In vitro chemotaxis was examined by a modification of Boyden's method using a membrane filter, 3 μ in pore size. Culture filtrate of *Escherichia coli* was used as a chemotactic factor. Incubation time was four hours for capillary tube migration assay, and it was three hours for random filter mobility and chemotactic assays. Random tube mobility was measured by migration distance. To evaluate random filter mobility or chemotaxis, the index was calculated by dividing the number of neutrophils in ten fields of finished side by that of starting side (×1,000). Random mobility and chemotaxis were studied four times. Nitro blue tetrazolium dye (NBT) reaction was done according to the method of Park et al.[6] Phagocytic and bactericidal abilities against *Staphylococcus aureus* were estimated by the method of Tan et al.[7]

RESULTS

As described earlier, the absolute neutrophilic counts continued to be less than 300/cu mm until 15½ months of age. At 16 months of age, the neutrophilic counts increased to normal range and they have remained at the normal range thereafter (Fig 1). No structural abnormality of neutrophils was found on either light or electron microscopy. The response to epinephrine was poor: epinephrine stimulation increased the absolute neutrophilic count from 288/cu mm to 1,200/cu mm, which was less than the lowest limit of normal response of 2,200/cu mm.[8] The hydrocortisone administration increased the absolute neutrophilic count from 107/cu mm to 696/cu mm. The in vivo leukocyte migration study by Rebuck and Crowley[4] showed migration of only a few neutrophils. Migration of mononuclear cells was normal. Results of neutrophilic random mobility and chemotaxis are given in the Table. When studied at 8, 10, and 11 months of age, random tube migration of the patient's neutrophils in each study was impaired: values of migration distance of the patient's cells were between 6.2 and 7.5 mm as compared with that of control cells of 15.0 ± 1.0 mm. The random filter mobility index of the patient's neutrophils was 86 at 8 months of age, which was only 23% of that of control cells (380 ± 30). In control children, the neutrophilic chemotactic index was relatively constant when the cell suspension was prepared at concentrations of 5×10^5 to 2×10^6 cells per milliliter. The cell concentration was adjusted, therefore, to be 5×10^5 cells per milliliter in every experiment of the present chemotactic study. The patient's chemotaxis was defective during infancy: the patient's values were between 90 and 161 cells per milliliter as compared with the control value of

409 ± 84. When studied at 16 months of age, the random migration and chemotaxis were normal. The NBT test result was normal. The phagocytic and bactericidal abilities were normal.

COMMENT

Our patient had recurrent tonsillitis and stomatitis, but he had no severe pyogenic infection. Severe neutropenia and defective neurophilic mobility were observed during infancy, and they were found to be normal when he was 16 months of age. Neutrophils were normal in structure. Bone marrow examination showed a normal number of mature neutrophils. Stimulation with epinephrine or hydrocortisone increased the neutrophilic counts, but peak increases were lower as compared with normal values.

In 1971, Miller and co-workers[1] described two cases of "lazy-leukocyte" syndrome, and in 1975, Constantopoulos et al[2] reported another case. The "lazy-leukocyte" syndrome is characterized by recurrent infections, severe neutropenia, normal bone marrow reserve, and defective neutrophilic random mobility and chemotaxis. In the disorder, neutrophilic response on stimulation with epinephrine or hydrocortisone is poor. The clinical and laboratory features of "lazy-leukocyte" syndrome appear identical to those of our patient during infancy. Initially, therefore, the diagnosis of "lazy-leukocyte" syndrome was made.

It is of interest that the neutropenia and defective neutrophilic mobility were improved at 16 months of age in our patient. In recent years, ascorbic acid has been demonstrated to improve neutrophilic functions[9] including neutrophilic mobility. Our patient was treated with ascorbic acid, and the neutrophilic count and mobility were improved after an increase of its dosage from 200 mg to 400 mg daily. It is unlikely, however, that the improvement in neutrophilic count and function is directly due to ascorbic acid because a decrease in dosage and even discontinuation of the drug did not reduce the cell count.

Spontaneous recovery from neutropenia has been demonstrated in several patients with chronic benign neutropenia.[10-12] Salmonssen[10] described a patient with neutropenia and episodes of catarrhal infection, mouth ulcer, and stomatitis. The disease was self-limited, beginning at 2½ years of age. Similar cases were also reported by other.[11,12] In chronic benign neutropenia, bone marrow is normal or lacks fully matured neutrophils.[11] In the disorder, unfortunately, the detailed studies are lacking in the functions of neutrophilic mobility.[12] For our patient, therefore, the diagnosis of chronic benign neutropenia might be made on the basis of the benign clinical course, transient neutropenia, and normal marrow, unless neutrophilic functions were studied.

Because of lack of studies on "lazy-leukocyte" syndrome for a period of years and the lack of neutrophilic function studies on chronic benign neutropenia, the difference between the two disorders is still obscure. The present report demonstrates a case in which not only the neutrophilic count but also its mobility underwent spontaneous normalization and further suggests that the disorder is transient "lazy-leukocyte" syndrome during infancy.

Nonproprietary Name and Trademark of Drug

Streptokinase-streptodornase—*Varidase.*

References

1. Miller ME, Oski FA, Harris MB: Lazy-leucocyte syndrome: A new disorder of neutrophil function. *Lancet* 1:665-669, 1971.
2. Constantopoulos A, Karpathios T, Nicolaidou P, et al: Lazy leukocyte syndrome: A case report. *J Pediatr* 87:945-946, 1975.
3. Komiyama A, Morosawa H, Akabane T, et al: Abnormal neutrophil maturation in a neutrophil defect with morphologic abnormality and impaired function. *J Pediatr* 94:19-25, 1979.
4. Rebuck JW, Crowley JH: A method of studying leukocyte functions in vivo. *Ann NY Acad Sci* 59:757-805, 1955.
5. Bryant RE, DesPrez RM, VanWay MH, et al: Studies on human leukocyte motility. *J Exp Med* 124:483-499, 1966.
6. Park BH, Fikrig SM, Smithwick EM: Infection and nitroblue-tetrazolium reduction by neutrophils. *Lancet* 2:532-534, 1968.
7. Tan JS, Watanakunakorn C, Phair JP: A modified assay of neutrophil function: Use of lysostaphin to differentiate defective phagocytosis from impaired intracellular killing. *J Lab Clin Med* 78:316-322, 1972.
8. Falk PM, Rich K, Feig S, et al: Evaluation of congenital neutropenic disorders by in vitro bone marrow culture. *Pediatrics* 59:739-748, 1977.
9. Boxer LA, Watanabe AM, Rister M, et al: Correction of leukocyte function in Chediak-Higashi syndrome by ascorbate. *N Engl J Med* 295:1041-1045, 1976.
10. Salmonssen L: Granulocytopenia in children. *Acta Pediatr* 35:189-201, 1948.
11. Vahlquist B, Anjou N: Granulocytopénie chronique bénigne. *Acta Haematol* 8:199-208, 1952.
12. Pincus SH, Boxer LA, Stossel TP: Chronic neutropenia in childhood: Analysis of 16 cases and a review of the literature. *Am J Med* 61:849-861, 1976.

Phenotypic Variation in a Family With Partial Androgen Insensitivity Syndrome

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• **A family with partial androgen insensitivity syndrome exhibited considerable variation in phenotypic expression of their androgen resistance. One subject died at 2½ years of age of a Wilms' tumor. In the two living members, one had a micropenis with otherwise normal genitalia, while the other had a small phallus, perineoscrotal hypospadias, bifid scrotum, and persistence of a vaginoutricular pouch. At puberty, plasma androgens and serum gonadotropins increased to normal or elevated values. However, despite adequate endogenous plasma testosterone levels and testosterone therapy, these patients showed poor virilization and were sterile. Studies of cultured sexual skin fibroblasts showed adequate 5α-reductase activity and normal receptor affinity and capacity for dihydrotestosterone. An X-linked mode of inheritance is postulated, although autosomal dominance cannot be ruled out.**

(*Am J Dis Child* 134:470-473, 1980)

Among the variety of disorders leading to male pseudohermaphroditism, end-organ resistance to androgens has been characterized in detail. In 5α-reductase deficiency, absence of the intracellular enzyme that converts testosterone to dihydrotestosterone (DHT) is believed to be the cause of androgen resistance.[1,2] We have recently reported that complete androgen insensitivity syndrome (CAIS), or testicular feminization, was due to the absence of androgen receptor activity in sexual skin fibroblasts.[3] However, some subjects with CAIS have normal receptor activity, and it has been postulated that their androgen resistance is due to an abnormality of the binding of the DHT-receptor complex to the specific acceptor site on chromatin.[4] In some patients with partial androgen insensitivity syndrome (PAIS), the degree of DHT binding in cultured skin fibroblasts is definitely below normal values but not completely absent.[5,6] However, other subjects with PAIS have perfectly normal DHT binding.[6,7] Clinically, patients with PAIS have variable phenotypic expression of their androgen resistance ranging from severe pseudohermaphroditism to normal phenotypes with defective spermatogenesis as reported by Bowen et al,[8] Wilson et al,[9] and Aiman et al.[10]

In the present study, we describe a family with PAIS in whom the three affected members showed different clinical manifestations of their androgen resistance. Furthermore, one patient had a Wilms' tumor. Studies of their plasma androgen and serum gonadotropin levels, testosterone metabolism, and binding by skin fibroblasts are reported along with their response to testosterone therapy.

METHODS

Plasma levels of testosterone,[11] androstenedione,[6] progesterone, 17α-hydroxyprogesterone,[12] serum luteinizing hormone (LH),[13] and follicle-stimulating hormone (FSH)[14] were measured by radioimmunoassay as previously described. The fibroblast culture procedure and the DHT receptor and 5α-reductase assays were reported previously.[6]

REPORT OF CASES

The pedigree of the family is shown in Fig 1.

Case 1.—The case of the maternal "aunt" of the proband (III-3) was evaluated elsewhere. This patient (II-9) was reared as a female because the external genitalia appeared female except for posterior fusion of the labia and the presence of a urogenital sinus. The patient died at 2½ years of age of a Wilms' tumor located in the right kidney. At an autopsy at District of Columbia General Hospital, Washington, DC, metastases were found to extend to the pleura, peritoneum, and pelvis. A mass in the left labia majora was found to be a testis with vas deferens. On microscopic examination, the testis appeared immature. No Barr chromatin bodies were observed in any of the tissues examined, including the two kidneys, Wilms' tumor, and pancreas. There was no evidence of a right gonad, and no genital ducts could be identified.

Case 2.—The patient (III-3) was a 3.230 kg, full-term infant. The pregnancy and delivery were normal. At delivery, he was noted to have a small penis and was reared as a male. At age 3 years, the family physician was concerned about the development of the patient's penis, and a urologic investigation was arranged. The results of a cystoscopic examination, an intravenous pyelogram (IVP), and a testicular biopsy were normal. The results of a buccal smear were negative for Barr chromatin bodies, and his karotype was 46, XY.

At age 3 years 8 months, he was referred to The Johns Hopkins Hospital, Baltimore, for possible treatment of his micropenis. His physical examination, including height and weight, was normal except for a bilateral varus foot deformity and a small penis that measured 2 cm in length when stretched (Fig 2). The urethral opening was normally located at the tip of the penis, and the testes were in the scrotum, which

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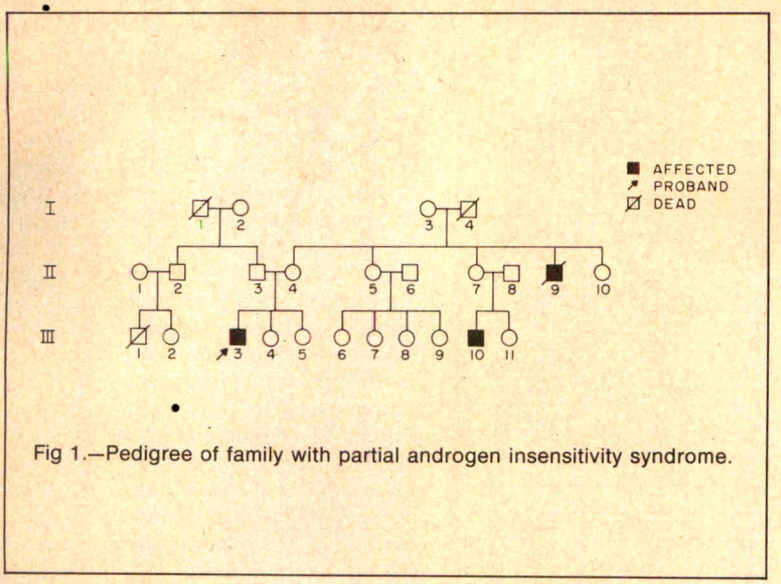

Fig 1.—Pedigree of family with partial androgen insensitivity syndrome.

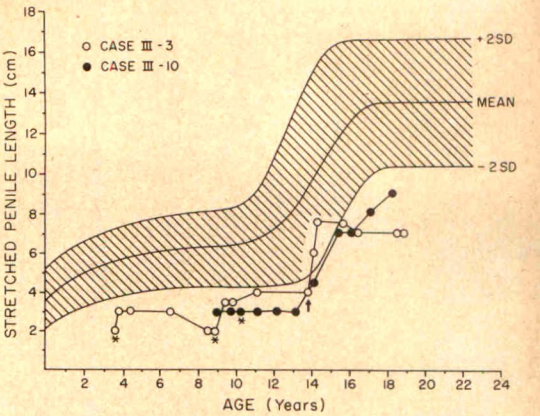

Fig 2.—Penile growth of subjects III-3 and III-10 compared with normal mean ± 2 SD (shaded area). Subject III-3 was treated twice with 0.2% testosterone cream (*) and with intramuscular testosterone enanthate injections (↑). Subject III-10 was treated for four months with testosterone cream (*). Normal stretched penile lengths were derived from Schonfeld.[24]

measured 2¼ × 1¼ cm bilaterally. There was a prominent scrotal raphe. Bone age was consistent with chronological and height ages. At that time, topical therapy with 0.2% testosterone cream was administered three times a day for four months. This resulted in penile enlargement to 3.0 cm stretched length and the appearance of a minimal amount of pubic hair. This response was less than that usually seen.

At 8½ years of age, penile length had regressed to about 2 cm (Fig 3), and topical treatment was reinstated for a 16-month period. Although the penis rapidly grew to 3.5 cm, no additional growth was observed at 9 years 10 months of age, and therapy was stopped.

Because of severe psychological problems related to penile size, therapy with 200 mg of intramuscular testosterone enanthate every four weeks was started at 13 years 10 months of age. Prior to this therapy, his penis measured 4 cm stretched length and 1.5 cm in diameter. His plasma testosterone level was 39 ng/dL (Table). After six months of treatment, his penis increased to 7.5 cm in length, and treatment was discontinued. Also, pubic and axillary hair appeared (Tanner stage 2). Subsequent examination showed no further penile growth (Fig 2).

At age 18 years 10 months, his right testis measured 3.6 by 2.2 cm, and his left measured 4.2 × 2.2 cm. Pubic hair of female distribution and axillary hair were at Tanner stage 4. Minimal bilateral gynecomastia was present. A semen sample, with a total volume of less than 0.25 mL, contained no sperm. His serum LH level was 121 ng/mL, 5 SD above the mean for a normal adult male (Table), and his serum FSH level was 403 ng/mL, 2.5 SD above the mean for a normal adult male. His plasma testosterone level was 738 ng/dL, which is in the normal range for adult males. Plasma progesterone level was 51 ng/dL (mean ± SD for normal adult males, 26 ± 4 ng/dL), and 17α-hydroxyprogesterone level was 341 ng/dL (mean ± SD for normal adult males, 94 ± 23 ng/dL). A pubic skin biopsy specimen was obtained to establish fibroblast monolayers to assess 5α-reductase and DHT-binding activity. The amount of 5α-reduced steroids after 30 minutes of incubation with testosterone was 648 pg/μg DNA, and after 60 minutes, it was 725 pg/μg DNA. These values were within the range for normal subjects.[6] A Scatchard plot, analyzed by linear regression of a DHT saturation curve, gave a maximum binding capacity of 306 moles × 10^{-18}/μg DNA and an apparent dissociation constant of 0.78 × 10^{-9}M. These values are in the normal range for our assay.[6]

Case 3.—The patient (III-10) was the maternal first cousin of patient 2 (III-3) and was a 3.970-kg infant. The pregnancy was complicated by polyhydraminos. The delivery was normal, but at birth the following physical anomalies were noted: a large head (head circumference, 37 cm, 98th percentile) with a frontal bossing, large tongue, and short blunted hands and feet. Body length was 57 cm, which is above the 98th percentile. The external genitalia were ambiguous. There was a small penis with chordee and perineoscrotal hypospadias. Only the right gonad could be felt in the bifid scrotum. The results of a buccal smear were negative for Barr chromatin bodies, and the karyotype was 46, XY. At 4 years of age, a retrograde cystourethrogram showed the presence of a rudimentary vaginal pouch that opened posteriorly and proximal to the external urethral sphincter. An exploratory laparotomy showed that both of the vasa deferentia were connected to the vaginal pouch and had to be resected when the pouch was removed. No left gonad could be found at that time. The histologic examination of a biopsy specimen from the right gonad showed an immature testis. The patient was subsequently admitted to a hospital on several occasions for repair of the hypospadias.

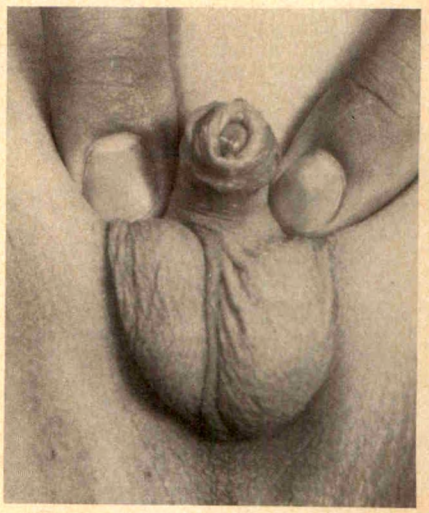

Fig 3.—Genitalia of subject III-3 at age 8½ years showing micropenis and prominent scrotal raphe. Testes are within scrotum.

He was first examined at The Johns Hopkins Hospital, Baltimore, at the age of

Serum Concentrations of Luteinizing (LH) and Follicle-stimulating (FSH) Hormones and Plasma Concentrations of Testosterone (T) and Androstenedione (Δ)

	Age, yr, mo	LH, ng/mL	FSH, ng/mL	T, ng/dL	Δ, ng/dL
Patient III-3	9,10	20	...	0	25
	13,10	18	130	39	...
	14,11	50	459*	189	...
	15,8	58	413*	231	80
	16,2†	89*	389*	219	95
	16,2‡	...	...	748	101
	16,6	71	341	330	...
	18,7	119*	484*	724	134
	18,10	121*	403*	738	105
Patient III-10	9,0	34	60	10	106
	11,2	23	78	40	...
	13,2	38	231	...	...
	15,6	78	535*	1,040*	...
	16,2	66	424*	1,114*	158*
	18,4	49	453*	1,189*	161*
Normal adult males, mean ± 1 SD	...	50 ± 14	187 ± 89	575 ± 150	109 ± 20

*Indicates that the values are 2 SD or more above the mean for normal adult males.
†Concentrations were measured before 3,000 IU/sq m/day of human chorionic gonadotropin was administered intramuscularly for six days.
‡Concentrations were measured after treatment with human chorionic gonadotropin.

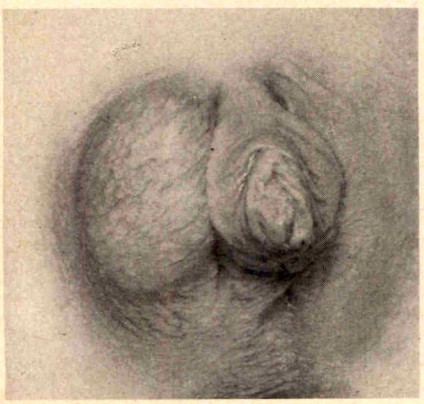

Fig 4.—Genitalia of subject III-10 at age 9 years showing small phallus, bifid scrotum, and absence of left testis.

9 years. His height was 149.2 cm (height age, 11 years, 7 months), and his weight was 52.2 kg. The same abnormalities of the face and extremities that were present at birth were noted. His penis measured 3 cm in length (Fig 2). The scrotum was bifid and contained only the right testis, which measured 1.25 × 0.75 cm (Fig 4). There was no sexual hair present. His serum LH level was 34 ng/mL, FSH level was 60 ng/mL, and plasma testosterone level was 10 ng/dL (Table). A five-month trial of topical 0.2% testosterone cream did not result in any appreciable growth of his penis (Fig 2).

Several investigations were performed in an attempt to rule out metabolic or endocrine disorders and cerebral gigantism. Renal function studies, including the results of urinalysis and an IVP, and serum creatinine and BUN levels, were normal. The protein-bound iodine, T_4 by column, and tests for urinary mucopolysaccharides showed normal results. There was a normal plasma growth hormone response to 0.5 g/kg of arginine hydrochloride in a 10% solution and to stimulation with 0.075 μ/kg of insulin (administered intravenously), and there was no paradoxical rise after glucose load. His scores on the Wechsler Intelligence Scale for Children showed a full IQ of 100.

Subsequent serum LH, FSH, and plasma testosterone determinations showed a progressive increase over the next six years (Table). A left testis, located in the inguinal canal, was first palpated at age 15½ years and was brought down surgically at 17 years, 4 months. At the time of orchiopexy, skin was obtained from the penis and the scrotum to establish fibroblast monolayers. 5α-Reductase activity was found to be normal: penile skin fibroblasts were normal at 993 pg/μg DNA at 30 minutes and at 1,260 pg/μg DNA at 60 minutes, and scrotal skin fibroblasts were normal at 559 pg/μg DNA at 30 minutes and at 976 pg/μg DNA at 60 minutes. The binding capacity and apparent dissociation constant of the DHT receptor from fibroblasts of the penis were 622 moles × 10^{-18}/μg DNA and 1.13 × 10^{-9}M, respectively. These values were within our normal range.[6] The scrotal fibroblasts also had normal DHT-receptors at 648 moles × 10^{-18}/μg DNA, with a high normal K_d at 2.78 × 10^{-9}M.

At age 18 years 4 months, his stretched penis measured 9 cm in length. His left testis measured 5.0 × 2.5 cm and the right measured 7.0 × 3.5 cm. Previous examinations over several years had also indicated a notable discrepancy in testicular size, with the right testis (which had been palpable throughout life) considerably larger, suggesting compensatory hypertrophy. The nipples were prominent, and the breasts were large and consisted mainly of adipose tissue. Pubic and axillary hair were at Tanner stage 5, with a normal male distribution. The beard was light and required shaving less than once a week. Plasma progesterone level was 21 ng/dL, which is in the normal range for adult males, while plasma 17α-hydroxyprogesterone level was 150 ng/dL, which is 2 SD above the normal mean.

COMMENT

The three patients described in the present report had various degrees of male pseudohermaphroditism. Patient III-3 had abnormally high levels of serum LH and FSH, while the plasma testosterone level was in the range for normal adult males. Patient III-10 had plasma androgen levels well above the normal range, with an abnormally high serum FSH level but a normal serum LH level. The finding of normal plasma testosterone levels combined with high LH or increased plasma testosterone levels and incomplete masculinization of the external genitalia suggests partial insensitivity to the action of androgens at the level of androgen-sensitive tissues, including the hypothalamus and pituitary. Plasma progesterone and 17α-hydroxyprogesterone levels were increased in patient III-3, but enzyme deficiency is unlikely because this patient had complete genital virilization but inadequate penile growth. For both of these patients, 5α-reductase activity in sexual skin fibroblasts was within the normal range, indicating that there was no defect in the conversion of testosterone to DHT in normally androgen-responsive tissues. Thus, these data suggest these patients have the incomplete form of androgen insensitivity, which was previously called Reifenstein's syndrome.[15] The patients had normal DHT-binding capacities, as did the previously reported cases,[6,7] and the cause of

their androgen insensitivity is unknown at present.

The phenotype of PAIS includes hypospadias with partial masculinization of external genitalia, gynecomastia, incomplete virilization at puberty, and sterility.[8,9] In this family with PAIS, affected members had variable phenotypic expression of androgen resistance, as previously noted by Wilson et al.[9] Their clinical phenotype varied from notable ambiguity of the genitalia (case 1, II-9) to almost complete masculinization (case 2, III-3). Minimal breast tissue could be palpated in both patients. During infancy and childhood, systemic and/or topical therapy with testosterone resulted in limited penile growth in patient III-3 and none in patient III-10. At puberty, despite adequate or excessive levels of endogenous plasma testosterone, penile length remained 2 SD below the normal mean for both subjects. The partial virilizing effects that occurred despite normal or high levels of plasma androgens are additional evidence for partial androgen resistance. Both patients are infertile: case III-3 had no sperm when semen was analyzed, and case III-10 had at least mechanical sterility since the distal portion of vasa deferentia was resected during removal of the vaginal pouch. Testicular biopsy to determine spermatogenesis was not done.

The combination of Wilms' tumor with or without nephron disorders and various types of male pseudohermaphroditism has been previously reported.[16-21] Because the kidneys and gonads arise from neighboring anlage, the ambiguous genitalia associated with Wilms' tumors are probably due to a primary injury of the gonadal anlage. In contrast, in our patient II-9, the family history suggests that the abnormal genitalia may have been due to a defect of the androgen receptors in target cells and that the Wilms' tumor was perhaps coincidental.

Total failure of virilization is seen in patients with CAIS. Two genetic variants have been described. One of them has deficient cytoplasmic androgen binding[3-5] that results from a mutation of the X-linked gene that specifies the DHT receptor,[22] as described in humans and the tfm/Y mouse.[23] The second variant has quantitatively normal specific cytoplasmic DHT binding in fibroblasts, and their defect is unknown, their pattern of transmission being compatible with either X-linked or sex-limited autosomal dominant inheritance,[4] the latter of which is less likely.

In PAIS, the level of DHT-receptor activity lies between normal levels and those of persons with CAIS[5,6] among some patients. Other patients have a similar phenotype, including partially masculinized external genitalia concomitant with increased plasma levels of androgens and gonadotropins but normal levels of DHT-receptor activity.[6,7] Both groups of patients respond poorly to androgen therapy. By analogy with the two variants of CAIS, patients with PAIS and normal DHT receptors are considered to have a partial form of the second variant of CAIS, like in the present family, which showed some response to testosterone therapy.

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Stephen Rothwell provided technical assistance and Barbara S. Mace provided secretarial assistance.

Nonproprietary Name and Trademarks of Drug

Arginine hydrochloride—*Argivene, R-Gene.*

References

1. Walsh PC, Madden JD, Harrod MJ, et al: Familial incomplete male pseudohermaphroditism, type 2. *N Engl J Med* 291:944-949, 1974.

2. Imperato-McGinley J, Gautier T, Peterson RE: Steroid 5α-reductase deficiency in man: An inherited form of male pseudohermaphroditism. *Science* 186:1213-1214, 1974.

3. Keenan BS, Meyer WJ, Hadjian AJ, et al: Syndrome of androgen resistance in man: Absence of 5α-dihydrotestosterone binding protein in skin fibroblasts. *J Clin Endocrinol Metab* 38:1143-1146, 1974.

4. Amrhein JA, Meyer WJ, Jones HW, et al: Androgen insensitivity in man: Evidence for genetic heterogeneity. *Proc Natl Acad Sci USA* 73:891-894, 1976.

5. Griffin JE, Punyashthiti K, Wilson JD: Dihydrotestosterone binding by cultured human fibroblasts: Comparison of cells from control subjects and from patients with hereditary male pseudohermaphroditism due to androgen resistance. *J Clin Invest* 57:1342-1351, 1976.

6. Amrhein JA, Klingensmith GJ, Walsh PC, et al: Partial androgen insensitivity: The Reifenstein syndrome revisited. *N Engl J Med* 297:350-356, 1977.

7. Keenan BS, Kirkland JL, Kirkland RT, et al: Male pseudohermaphroditism with partial androgen insensitivity. *Pediatrics* 59:224-231, 1977.

8. Bowen P, Lee CSN, Migeon CJ, et al: Hereditary male pseudohermaphroditism with hypogonadism, hypospadias, and gynecomastia (Reifenstein's syndrome). *Ann Intern Med* 62:252-270, 1965.

9. Wilson JD, Harrod MJ, Goldstein JL, et al: Familial incomplete male pseudohermaphroditism, type 1: Evidence for androgen resistance and variable clinical manifestations in a family with the Reifenstein syndrome. *N Engl J Med* 290:1097-1103, 1974.

10. Aiman J, Griffin JE, Gazak JM, et al: Androgen insensitivity as a cause of infertility in otherwise normal men. *N Engl J Med* 300:223-227, 1979.

11. De Lacerda L, Kowarski AA, Johanson AL, et al: Integrated concentration and circadian variation of plasma testosterone in normal men. *J Clin Endocrinol Metab* 37:366-371, 1973.

12. Gutai JP, Meyer WJ, Kowarski AA, et al: Twenty-four-hour integrated concentrations of progesterone, 17-hydroxyprogesterone, and cortisol in normal male subjects. *J Clin Endocrinol Metab* 44:116-120, 1977.

13. Lee PA, Plotnick LP, Steele RE, et al: Integrated concentrations of luteinizing hormone and puberty. *J Clin Endocrinol Metab* 43:168-172, 1976.

14. Lee PA, Plotnick LP, Migeon CJ, et al: Integrated concentrations of follicle-stimulating hormone and puberty. *J Clin Endocrinol Metab* 46:488-490, 1978.

15. Bowen P, Lee CSN, Migeon CJ, et al: Hereditary male pseudohermaphroditism with hypogonadism, hypospadius, and gyneiomastia (Reifenstein's syndrome). *Ann Intern Med* 62:252-270, 1965.

16. Raubitschek H: Über eine bösartige nierengeschwulst bei einem kindlichen hermaphroditen. *Frankfurt Z Pathol* 10:206-218, 1912.

17. Stump TA, Garret RA: Bilateral Wilms' tumor in a male pseudohermaphrodite. *J Urol* 72:1146-1152, 1964.

18. Ångström T: Nephroblastoma in a case of agonadism. *Cancer* 18:857-862, 1965.

19. Denys P, Malvaux P, Van Den Berghe H, et al: Association d'un syndrome anatomo-pathologique de pseudohermaphroditisme masculin, d'une tumeur de Wilms, d'une néphropathie parenchymateuse et d'un mosaicisme XX/XY. *Arch Fr Pediatr* 24:729-739, 1967.

20. Drash A, Sherman F, Hartmann WH, et al: A syndrome of pseudohermaphroditism, Wilms's tumor, hypertension, and degenerative renal disease. *J Pediatr* 76:585-593, 1970.

21. Barakat YA, Papadopoulos ZL, Chandra RS, et al: Pseudohermaphroditism, nephron disorder, and Wilms' tumor: A unifying concept. *Pediatrics* 54:366-369, 1975.

22. Meyer WJ, Migeon BR, Migeon CJ: Locus on human X chromosome for dihydrotestosterone receptor and androgen insensitivity. *Proc Natl Acad Sci USA* 72:1469-1472, 1975.

23. Lyon MF, Hawkes SG: X-Linked gene for testicular feminization in the mouse. *Nature* 227:1217-1219, 1970.

24. Schonfeld WA: Primary and secondary sexual characteristics: Study of their development in males from birth through maturity, with biometric study of penis and testes. *Am J Dis Child* 65:535-549, 1943.

Management of Acute Asthma in Childhood

A Randomized Evaluation of β-Adrenergic Agents

Alan L. Schwartz, PhD, MD; Jeffrey M. Lipton, MD, PhD; David Warburton, MB; Lawrence B. Johnson, MD; Frank J. Twarog, MD, PhD

• **We examined the efficacy of several β-adrenergic agents commonly used to treat asthma and evaluated the optimum route of administration. Two hundred and sixty-nine persons aged 5 to 21 years who came to the emergency ward while suffering from acute asthma were treated with either (1) inhalation isoetharine hydrochloride or (2) subcutaneous epinephrine or terbutaline sulfate. Patients were evaluated using clinical scores and pulmonary function tests and were monitored for adverse side effects. Regardless of mode of therapy, the acute attack was either treated successfully, terminated in hospital admission, or required further therapy within 24 hours in a comparable number of patients. Adverse side effects were more common with terbutaline sulfate than with either epinephrine or isoetharine in the doses used. Thus, inhalation of β-adrenergic agents is as effective as subcutaneous administration in the treatment of acute asthma in childhood.**

(*Am J Dis Child* 134:474-478, 1980)

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Acute asthmatic attacks constitute a major therapeutic problem in the physician's office and the emergency ward. Recommended guidelines for treatment have been published.[1-3] However, the availability of new β-2 selective adrenergic agents[4,5] necessitates a reevaluation of recommended regimens. The purpose of this study was twofold: first, to compare the efficacy of subcutaneous epinephrine with terbutaline sulfate; and second, to compare routes of administration of adrenergic agents (subcutaneous vs inhaled) in an acute care setting.

Subjective and objective criteria were used to assess the efficacy of each regimen and to monitor for adverse side effects. The results have demonstrated equivalent efficacy for all regimens studied. Thus, inhalation of β-adrenergic agents is as effective as subcutaneous administration.

MATERIALS AND METHODS

Treatment Protocols

Parenteral.—Epinephrine and terbutaline sulfate were prepared in double-blind coded vials by our pharmacy at a concentration of 1 mg/mL (Fig 1). These agents were administered at 15-minute intervals to a total of three doses (0.01 mg/kg, with a maximum dose of 0.4 mL). When required, further therapy was provided by inhaled isoetharine hydrochloride (Bronkosol). After two doses of isoetharine, aminophylline was administered intravenously (5 to 7 mg/kg during 20-minute period), if clinically indicated. Ten minutes after completion of the aminophylline administration, a decision regarding discharge or admission to hospital was made by the house officer and senior resident in charge of the emergency ward.

At any stage in this regimen, treatment was discontinued and the patient discharged from the emergency ward when he/she was clinically judged to be free of asthma by resolution of respiratory distress and improvement in auscultatory findings. Neither clinical scoring nor pulmonary function measurement was used in this clinical decision, as it was not known in advance what degree of improvement in these measurements would correlate with clinical resolution of asthma. Patients were given epinephrine (Susphrine) (0.005 mL/kg) and a dose of oral theophylline (5 mg/kg) before discharge if no intravenous (IV) aminophylline had been administered.

Inhalation.—Therapy was provided by inhalation of 0.5 mL of isoetharine hydrochloride in 2 mL of saline solution delivered by intermittent positive pressure breathing (IPPB) using a respirator powered with 40% oxygen at a pressure of approximately 15 cm H_2O. This was repeated when necessary for a total of three treatments at 20-minute intervals. Further therapy included up to two doses of a subcutaneous adrenergic agent (double-blind) and, if required, IV aminophylline. Discharge or admission was managed as outlined previously.

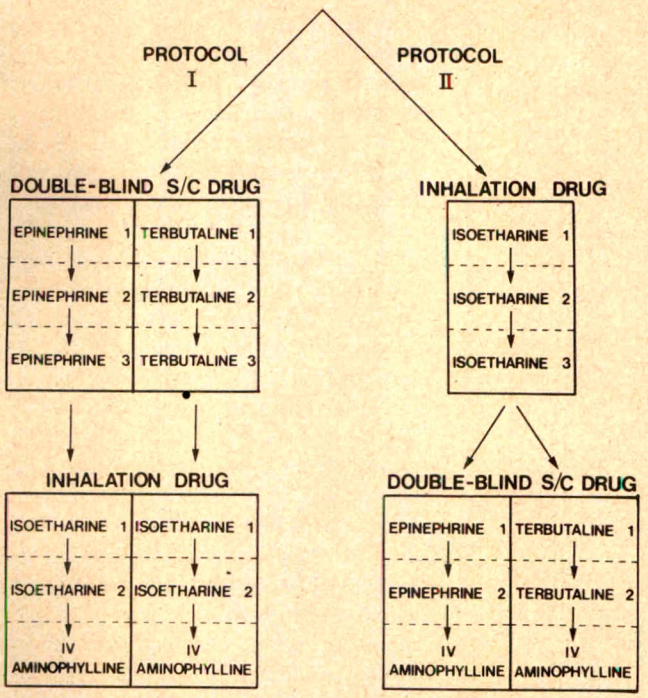

Fig 1.—Protocol for treatment of acute asthma. S/C indicates subcutaneous; IV, intravenous.

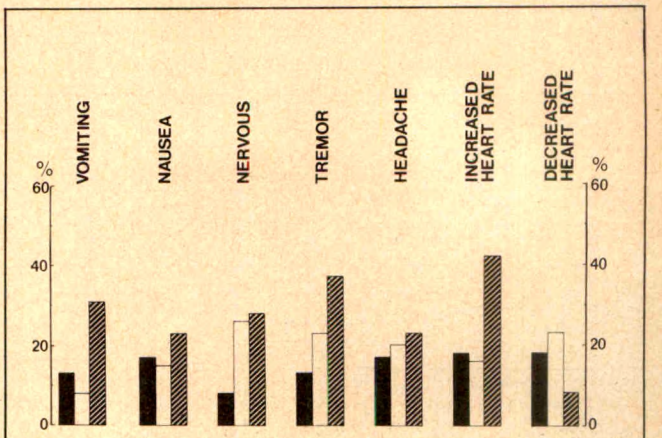

Fig 2.—Frequency of adverse side effects in patients receiving isoetharine hydrochloride, epinephrine, or terbutaline sulfate. Side effects were evaluated only for the first administered drug in each protocol. Change of 20 beats per minute or more above or below pulse rate measured at time of admission was considered significantly increased or decreased rate, respectively. Total number of patients receiving each medication; isoetharine, 127 (solid bar); epinephrine, 61 (open bar); terbutaline, 66 (hatched bar).

Selection of Patients

Patients with a diagnosis of acute asthma who were between the ages of 5 and 21 years and who came to the emergency ward were eligible. They were excluded if they had received parenteral therapy for the present attack, were in "impending respiratory failure," were pregnant, or were experiencing their first attack of asthma. Informed consent was obtained and assignment made on a random basis to one of the three protocols (Fig 1).

During the four-month study period, 509 visits were made to the emergency ward for acute asthma by persons eligible for the study: (1) 10% (50/509) were judged to be "too ill" to participate, and 50% (25/50) of these were admitted to the hospital; (2) 35% (179/509) declined to participate in the study, and 13% (23/179) of this group were admitted to hospital; (3) 55% (280/509) enrolled in the study, of whom 6% (18/280) were admitted to hospital. Four patients (4/280) who volunteered for the study were withdrawn immediately after receiving their first medication and were admitted to the hospital. In addition, seven patients (7/280) were not evaluated due to lost vial codes.

The 269 visits included in this study comprised 188 individual patients: 82% of these were studied once; 9%, twice; 5%, three times; and 4%, four or more times. Complete data were obtained on 254 of

Table 1.—Clinical Scoring System for Evaluation of Acute Asthma

	Score			
	0	1	2	3
Wheezing	None	Terminal expiratory	Entire expiratory	Inspiratory and expiratory
Inspiratory-expiratory ratio	5/2	5/3-5/4	1/1	<1/1
Use of accessory muscles	None	+	+ +	+ + +
Cyanosis	None	...	...	Present
Cerebral function	Normal	...	...	Abnormal
Heart rate	≤108	>108	...	...
Respiratory rate	≤28	>28	...	...

Table 2.—Clinical Outcome of Various Treatment Protocols

	Protocol 1		Protocol 2	
	A	B	A	B
Phase 1* No. of patients discharged (%)	51 (77)	52 (68)	93 (73)	
Phase 2† No. of patients discharged (%)	13 (20)	17 (22)	18 (14)	11 (9)
No. of patients admitted to hospital (%)	2 (3)	7 (9)	4 (3)	1 (1)
Total (%)	**66** (100)	**76** (100)	**127** (100)	

*Group A of protocol 1 received epinephrine, whereas group B received terbutaline sulfate. Both groups of protocol 2 received isoetharine hydrochloride.

†Both groups of protocol 1 received isoetharine hydrochloride. Group A of protocol 2 received epinephrine, whereas group B received terbutaline sulfate.

Table 3.—Clinical Scores and FEV, Before and After the First Phase of Therapy*

	Therapeutic Drug		
	Epinephrine	Terbutaline Sulfate	Isoetharine Hydrochloride
Clinical score			
Pretreatment	6.68 ± 2.90†	6.81 ± 2.03	6.12 ± 2.72
Posttreatment	2.15 ± 1.69†	2.63 ± 2.28	2.61 ± 1.98
No. of patients	59	57	113
FEV_1 (% predicted)			
Pretreatment	28.3 ± 15.4	24.7 ± 18.4	27.3 ± 16.1
Posttreatment	48.0 ± 19.9	50.6 ± 24.0	46.3 ± 20.9
No. of patients	60	64	115

*Mean ± standard deviation. FEV_1 indicates measurement of forced expiratory volume in one s.
†$P < .005$, pretreatment vs posttreatment for each therapeutic modality.

these 269 visits. Eighty percent of all the patients were contacted by telephone within 24 to 36 hours to determine whether further therapy was required or had been obtained through other sources.

The factors precipitating an acute asthmatic episode are frequently multiple and are difficult to determine. Of the participants in this study, 22% (57/254) reported upper respiratory tract symptoms with or without fever preceding the onset of asthma. One patient had pneumonia.

One hundred and forty-two subjects (53%) were assigned to the parenteral protocol and 127 (47%) to the inhalation protocol. Epinephrine was given to 66 (47%) and terbutaline to 76 (54%) in the parenteral protocol.

Clinical Evaluation

The clinical scoring systems of Wood et al[6] and Pierson et al[7] were modified by the addition of one point for heart rate greater than 108 beats per minute and one point for respirations greater than 28/min (Table 1). This modification was devised after analysis of vital signs and measurement of forced expiratory volume in one s (FEV_1) for the first 30 subjects studied showed that heart rate greater than 108 beats per minute and respiratory rate greater than 28/min correlated with a significant decrease in FEV_1 ($P < .05$).

Clinical scores were obtained prior to each administration of medication and at the time of discharge or admission to hospital. Complaints of nausea, headache, or nervousness were recorded and observations were made for vomiting, tremor, or tachycardia during these examinations to monitor for adverse side effects. This clinical evaluation was performed by the house staff assigned to the emergency ward at the time of this study.

Pulmonary Function Testing

Pulmonary functions were measured using an electronic spirometer. Although parameters recorded included forced vital capacity, FEV_1, forced expiratory flow 25% to 75% (expressed as percent predicted for age and height), and peak expiratory flow (expressed as liters per s), only FEV_1 is presented as being representative of pulmonary status. The best result of two separate trials was recorded initially. Subsequent results were based on a single recording. Statistical comparisons were performed using Student's t test.

RESULTS

The acute asthmatic attack was successfully treated in 71% (196/276) of all subjects during the first phase of therapy. The percent of patients clinically improved and discharged from the emergency ward was similar for each treatment regimen (Table 2). These groups were comparable ($P > .05$) on the basis of both clinical scores and FEV_1 (Table 3). The conditions of approximately 25% of all the patients improved sufficiently to be discharged at each successive dose of medication administered during the first phase regardless of either the pharmacologic agent used or the route of administration.

The conditions of approximately another 20% improved with further adrenergic therapy in the second crossover phase. Only 26% (5/19) of all those who required IV aminophylline after administration of the adrenergic agents were subsequently discharged home. Treatment failures resulting in admission to the hospital occurred after each protocol.

Nine percent (24/255) of all those discharged returned for further acute care within 24 hours. Telephone follow-up of 80% of all the patients indicated that none were treated at other facilities. Returns were equally distributed among the different regimens and were nearly as common in subjects discharged after a single adrenergic agent (epinephrine, 4/51; terbutaline, 3/52; isoetharine, 8/93) as in those receiving both subcutaneous and inhalation drugs (epinephrine and isoetharine, 2/13; terbutaline and isoetharine, 2/17; isoetharine and epinephrine, 4/18; isoetharine and terbutaline, 1/11) during the first visit.

Of the 254 subjects, 169 (76%) from whom the information was available reported taking theophylline within 24 hours, and half of all these (83/169) within three hours prior to entry into the study (Table 4). These patients were equally distributed among all the treatment groups. Of those reportedly taking theophylline within three hours of emergency therapy, 78% were discharged after receiving only one drug, the same rate as that for the entire study population (209/269, 78%). The results of emergency treatment were comparable for persons receiving other outpatient medication regimens, except for those receiving corticosteroid preparations, of whom 93% responded to the first phase of therapy.

Clinical Score and Pulmonary Function Assessment

There was no statistical difference between the groups of patients when clinical scores and FEV_1 were compared ($P > .05$) (Table 3). The mean clinical score on entry into the study was greater than 6, and FEV_1 less than 30% of that predicted. There was a comparable and significant decrease in clinical score and increase in FEV_1 ($P < .005$) after the first phase of all three therapeutic regimens.

Adverse Side Effects

Adverse side effects were tabulated only for the first phase of therapy. Tremors, vomiting, and increases in

Table 4.—Asthma Medications Taken Within 24 Hours of Emergency Treatment

	Theophylline	β-Adrenergic Agent*	Disodium Chromoglycate	Corticosteroid	Combination Medication
No. of patients (%)	169/254 (67)	67/254 (26)	15/254 (6)	15/254 (6)	8/254 (3)
Hours since administration (±SD)	4.5 (±3.4)	7.1 (±8)	4.7 (±4.6)	9.7 (±7.2)	8.6 (±5.2)
Hours since administration, range	1-24	1-25	2-18	2-24	3-19
% Discharged after first phase of therapy	74	78	71	93	75

*Either oral or inhaled.

pulse rate occurred most frequently with terbutaline (Fig 2). Theophylline preparations taken within three hours of therapy did not increase the incidence of complications associated with the adrenergic therapy.

COMMENT

This clinical trial has demonstrated that epinephrine, terbutaline and isoetharine, all β-adrenergic agents, were equally effective in the treatment of acute asthma in children. Both the subcutaneous and the inhalation routes of administration proved to be equally effective. The conditions of similar numbers of patients in each therapeutic regimen were successfully treated or required further treatment and admission of the patient to the hospital. Furthermore, the conditions of a comparable percent of patients improved clinically, and the patients were discharged home at each sequential dose of medication administered in each of the regimens. Repeated administration of adrenergic agents in this age group is warranted as the conditions of a large number of patients improved sufficiently to allow discharge, even after the fourth dose. Return visits for further therapy within 24 hours occurred equally in all treatment groups. More rigorous control of postdischarge therapy with a bronchodilator may have reduced this rate of returns.

Frequency of adverse side effects was highest in those patients treated with terbutaline. Complications most frequently noted were tremor, vomiting, and tachycardia. The adverse effects observed were generally minor and did not require discontinuation of therapy. Others who compared the efficacy of terbutaline with epinephrine for the treatment of asthma[8-13] have also reported more frequent side effects with terbutaline.[8-10,12,14] These adverse reactions are dose-dependent in adults, with decreased frequency when the dose is reduced from 0.5 to 0.25 mg.[10,13,14] A similar decrease in reactions also might be expected in children with a reduction in dose or frequency of administration; however, our data do not allow us to determine whether the efficacy would be equivalent.

Although attacks could be treated effectively by either the parenteral or the inhaled routes, several factors should be considered when using inhaled adrenergic agents. An increase in hypoxemia that may be the result of aggravated ventilation perfusion mismatch occurs with inhaled adrenergic drugs.[15,16] This complication also occurs with aminophylline and epinephrine,[17,18] but may be avoided in either case by increasing the fraction of inspired oxygen.[15] Tachyphylaxis and even paradoxical bronchoconstriction have been reported to occur in patients who have abused inhaled adrenergic drugs.[19-21] Occasionally, bronchoconstriction occurs without previous abuse.[20,22,23] These factors should be recognized as a possible cause for inadequate response or deterioration in the course of therapy with inhaled adrenergic agents.

Equivalent bronchodilation has been demonstrated with adrenergic agents administered either by positive pressure or by nebulization.[24-27] Intermittent positive pressure breathing was used in this trial as it was the customary mode of aerosol delivery in our hospital at the time. At the present time, inhaled adrenergic aerosol agents are administered by nebulization. Although no complication occurred with the use of IPPB, pneumothorax may result from this mode of therapy and has been implicated in asthma deaths.[28]

Based on the results of this study, the following recommendations are made for the management of acute asthma in childhood: (1) There was no therapeutic difference among the adrenergic agents studied and, therefore, epinephrine, terbutaline, or isoetharine can be used with equal efficacy. However, to decrease the incidence of adverse side effects with terbutaline, the dose should be reduced or the interval between doses increased. (2) Repeated administration of adrenergic agents in this age group is warranted as a large proportion of patients responded even after the fourth dose. (3) Since adrenergic agents can be administered with equal efficacy either subcutaneously or by inhalation, the latter route of delivery should be considered as a reasonable alternative to the traditional subcutaneous epinephrine in the management of acute asthma in childhood. (4) In a patient unresponsive to repeated administration of an adrenergic agent, admission to hospital should be anticipated as administration of IV aminophylline is unlikely to result in sufficient reduction in symptoms to allow discharge. (5) As terbutaline is not presently recommended for use in children younger than 12 years of age, a decision with regard to potential benefits must be made for each individual case.[29] (6) Significant residual pulmonary function abnormalities persist in children who are clinically recovered from an acute episode of asthma, and therefore continued therapy with a bronchodilator after treatment is essential.

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Nonproprietary Names and Trademarks of Drugs

Isoetharine hydrochloride—*Bronkosol.*
Terbutaline sulfate—*Brethine, Bricanyl*

References

1. Bierman CW, Pierson WE: The pharmacologic management of status asthmaticus in children. *Pediatrics* 54:282-284, 1974.

2. Franklin W: Treatment of severe asthma. *N Engl J Med* 290:1469-1472, 1974.

3. Senior RM, Lefrak SS, Korenblat PE: Status asthmaticus. *JAMA* 231:1277-1279, 1975.

4. Campbell AB, Soyka L: Selective β_2-receptor agonists for the treatment of asthma: Therapeutic breakthrough or advertising ploy. *J Pediatr* 89:1020-1026, 1976.

5. Wilson AF, McPhillips JJ: Pharmacologic control of asthma. *Ann Rev Pharmacol Toxicol* 18:541-561, 1978.

6. Wood DW, Downes JJ, Lecks HI: Clinical scoring system for the diagnosis of respiratory failure. *Am J Dis Child* 123:227-228, 1972.

7. Pierson WE, Bierman CW, Kelley VC: A double-blind trial of corticosteroid therapy in status asthmaticus. *Pediatrics* 54:282-288, 1974.

8. Davis WJ, Pang LM, Chernack WJ, et al: Terbutaline in the treatment of acute asthma in childhood. *Chest* 72:614-617, 1977.

9. Sly RM, Badei B, Facisne S: Comparison of subcutaneous terbutaline with epinephrine in the treatment of asthma in children. *J Allergy Clin Immunol* 59:128-235, 1977.

10. Smith PR, Heurich AE, Leffler CT, et al: A comparative study of subcutaneously administered terbutaline and epinephrine in the treatment of acute bronchial asthma. *Chest* 71:129-134, 1977.

11. Sackner MA, Greeneltch N, Silva G, et al: Bronchodilator effects of terbutaline and epinephrine in obstructive lung disease. *Clin Pharmacol Ther* 16:499-506, 1974.

12. Amory DW, Burnham SC, Cheney FW: Comparison of the cardiopulmonary effects of subcutaneously administered epinephrine and terbutaline in patients with reversible lung disease. *Chest* 67:279-286, 1975.

13. Schwartz HS, Trauttein II, Goldstein AK: Acute effects of terbutaline of epinephrine on asthma. *J Allergy Clin Immunol* 58:516-522, 1976.

14. Sackner MA, Dougherty R, Watson H, et al: Hemodynamic effects of epinephrine and terbutaline in normal man. *Chest* 68:616-624, 1975.

15. Gazioglu K, Condemi J, Hyde RW, et al: Effect of isoproterenol on gas exchange during air and oxygen breathing in patients with asthma. *Am J Med* 50:185-190, 1970.

16. Chick TU, Nicholson DP, Johnson RL Jr: Effects of isoproterenol on distribution of ventilation and perfusion in asthma. *Am Rev Respir Dis* 107:869-873, 1973.

17. Jezek V, Direднik A, Stepanek J, et al: The effect of aminophylline on the respiration and pulmonary circulation. *Clin Sci* 38:549-554, 1970.

18. Hales CA, Kazemi H: Hypoxic vascular response of the lung: Effect of aminophylline and epinephrine. *Am Rev Respir Dis* 110:126-132, 1974.

19. Van Metre TE Jr: Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J Allergy Clin Immunol* 43:101-113, 1969.

20. Reisman RE: Asthma induced by adrenergic aerosols. *J All Clin Immunol* 46:162-177, 1970.

21. Paterson JW, Connoly ME, Davies DS, et al: Isoprenaline resistance and the use of pressurized aerosols in asthma. *Lancet* 2:426-429, 1978.

22. Keighley JF: Iatrogenic asthma associated with adrenergic aerosols. *Ann Intern Med* 65:985-995, 1966.

23. Trautlein J, Allegra I, Field J, et al: Paradoxic bronchospasm after inhalation of isoproterenol. *Chest* 70:711-714, 1976.

24. Chang N, Levison H: The effect of a nebulized bronchodilator administered with or without intermittent positive pressure breathing on ventilatory function in children with cystic fibrosis and asthma. *Am Rev Respir Dis* 106:867-872, 1972.

25. Smelzer TH, Barnett TB: Bronchodilator aerosol: Comparison of administration methods. *JAMA* 223:885-889, 1973.

26. Loren M, Chai H, Miklich D, et al: Comparison between simple nebulization and intermittent positive-pressure in asthmatic children with severe bronchospasm. *Chest* 72:145-147, 1977.

27. Weber RW, Petty WE, Nelson HS: Aerosolized terbutaline in asthmatics. *J Allergy Clin Immunol* 63:116-121, 1979.

28. Karetsky MS: Asthma mortality associated with pneumothorax and intermittent positive-pressure breathing. *Lancet* 1:828-829, 1975.

29. Unapproved uses of approved drugs: The physician, the package insert, and the FDA. Committee on Drugs. *Pediatrics* 62:262-264, 1978.

60 YEARS AGO IN THE AJDC

Water Retention in Pneumonia

Over a period of five years the authors observed cases of lobar pneumonia among children under 2 years of age in which the sudden defervescence of fever (by crisis) was accompanied by a loss of weight. This frequently occurred within 24 hours of the subsidence of fever and averaged 9.6 ounces among this group of twenty-eight children. There were twenty-two cases of lobar pneumonia in which the fever did not subside promptly or in which complications occurred. Among this group five had no weight loss, and the remainder lost weight gradually over a period of days.

The authors observe that this rapid resolution is associated with an increase in urine volume output as well as urinary chlorides and nitrogen. 1916 studies with a skin elastometer had demonstrated the presence of edema in both children and adults during bouts of pneumonia. The authors suggest water retention may be related to heat retention and that "with restoration of the water-binding power of the tissues to the normal . . . , water would be liberated for heat regulatory purposes. . . ." HERBERT O. LUSSKY, BS, MD, HUGO FRIED, BS, MD, The Otho S. A. Sprague Memorial Institute Laboratory, Children's Memorial Hospital (19:337, May 1920).

Diphtheria-Tetanus Skin Testing

Its Clinical Value for Delayed Hypersensitivity

Donald B. Kaufman, MD; Wanderley C. deMendonça, MD; Joel Newton, MD

• Skin testing as an in vivo means of evaluating cell-mediated immune function is extremely valuable. However, problems lie in selecting the appropriate antigens and interpreting the results. The suggestion that diphtheria-tetanus would provide a good antigen in infants and children was evaluated by comparing skin test observations with results of skin biopsy examinations. Thirteen subjects, seven of whom were immunodeficient, were evaluated by skin reactions and dermal biopsy specimens. Fifty percent of the immunodeficient patients had positive skin test reactions but had biopsy specimens that were not consistent with delayed-type hypersensitivity (DTH). Although all normal controls on whom biopsies were done had histologic DTH reactions, two had negative or equivocal skin reactions. Our data suggest, on the contrary, that delayed hypersensitivity testing with this antigen is not a good screening test for disorders of immunity or inflammation.

(*Am J Dis Child* 134:479-483, 1980)

Testing for cell-mediated immunity is one of the more important aspects of diagnosing immunodeficiency disorders. The most currently available techniques require sophisticated in vitro testing. However, the cutaneous delayed hypersensitivity reaction is a safe, reliable, and easily available test for in vivo screening. When properly performed, it can give useful information on cell-mediated immunity in general and on the inflammatory response.[1,2]

There are several limitations to this test. Prior exposure to the antigen tested must have occurred, a situation not always easy to assess and often not present in the very young. In young children where there is a general lack of exposure to the commonly used test antigens, such as streptokinase-streptodornase, monilia, and trichophyton, positive reactions in children younger than 6 years old for streptokinase-streptodornase, younger than 7 months old for monilia, and younger than 16 years old for trichophyton are not usually expected. In addition, children's skin often react differently from adult skin and the criteria for positive reactions may vary. Furthermore, the reaction must be read at various times since there are often three stages that can be recognized (immediate, Arthus-type, and delayed) and improper interpretation may lead to false-positive or false-negative results. The immediate reaction, which is a wheal and flare, occurs at around 20 minutes postinjection and may persist for up to two hours. It is an allergic-type reaction resulting from the activation of IgE antibodies and the release of vasoactive amines, such as histamine. The Arthus reaction occurs from two to eight hours after injection and is an antigen-antibody or immune complex reaction involving IgG and complement. It is primarily an acute inflammatory reaction. Often, this reaction may persist for 24 hours or longer making the reading of a delayed-type hypersensitivity (DTH) response at 48 hours difficult to interpret. The DTH response is a cellular immune response involving primarily lymphocyte sensitization and occurs between 48 and 72 hours.

Facktor et al[3] have previously pointed out some of the difficulties associated with skin test interpretation in their study using tetanus toxoid (TT). Approximately 63% of their patients demonstrated an immediate reaction and 32% an Arthus reaction, whereas only 74% showed a delayed hypersensitivity reaction.

Recently, Franz et al[4] reported on the use of diphtheria-TT as a skin test antigen for DTH in a pediatric population and suggested that this may be a useful test for assessing cell-mediated immunity (CMI). They studied 114 subjects of various ages. By their criteria, 100% of infants 7 to 12 months old had positive skin tests and 88%, including those without immunization, between 1 and 5 years of age. Since most infants are immunized with diphtheria-tetanus (DT) beginning at 1 to 2 months of age and a

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Table 1.—Observation of Delayed Hypersensitivity Reactions

Cases/Age, yr	Observed Reactions (Erythema-Induration), mm						Other DTH Reactions*	Comments
	24 hr		48 hr		72 hr			
Normal controls								
PPD:								
1/4	4	0	8	6	4	2	NA	...
2/27	0	0	8	6	10	8	NA	...
Diphtheria-tetanus								
3/9	0	0	0	4	0	4	+ (SK-SD)	...
4/7	7	6	10	4	0	4	+ (SK-SD)	...
5/5	30	15	54	15	15	7	NA	Immediate response
6/38	9	8	0	5	0	2	+ (Trychophyton)	...
7/36	0	0	0	0	0	0	+ (*Candida*)	No biopsy done
8/6	15	7	25	10	8	10	—	Immediate reaction
(1:100)	20	15	40	20	30	10		
(1:10)								
Patients, diagnosis								
9, SCID†/1.4	12	10	8	4	6	2	—	...
10, SCID/5	8	12	8	2	6	1	—	Immediate response
11, no defect/6	15	12	15	12	13	10	+ (*Candida*, SK-SD)	...
12, 3 deficiency/2	6	6	12	12	10	10	NA	...
13, chemotactic defect/7	0	0	7	4	7	5	+ (SK-SD)	...
14, SCID/1.6	0	0	1	1	0	0	—	No biopsy done
15, variable ID/24	0	0	0	0	0	0	—	Defective cell-mediated immunity and humoral immunity
(1:100)	5	5	6	6	6	6		
(1:10)								

*DTH indicates delayed-type hypersensitivity; +, positive DTH response; —, negative DTH response; NA, data not available.
†SCID indicates combined immunodeficiency; ID, immunodeficiency.

history is easily obtainable, a skin test for DTH could provide valuable information in evaluating potentially immunologically incompetent children.

Unfortunately, their report only assessed the presence or absence of skin reactivity and no objective evidence was presented to substantiate whether these were delayed hypersensitivity reactions or not. In addition, only two patients with immunodeficiency were studied, one having an antibody-deficiency syndrome. We, therefore, evaluated the DT skin test response by visual measurements and histologically by punch biopsy on a series of patients seen in our immunology clinic.

MATERIALS AND METHODS

Informed consent was obtained from patients undergoing intradermal skin testing and punch biopsy. All patients were tested for cell-mediated and humoral-mediated deficiency, as well as disorders of inflammatory responses by standard in vitro techniques. These tests included quantitative immunoglobulins, antibody titers, and a variety of antigens, including diphtheria, rubella and streptolysin O, E rosettes, phytohemagglutinin (PHA) response, complement, quantitative nitro blue tetrazolium assay, and chemotaxis. Only those patients with a documented history of diphtheria-pertussis-tetanus immunizations or a recall booster within one year of this study were included in this evaluation. Biopsy specimens were taken from two normal volunteers with positive

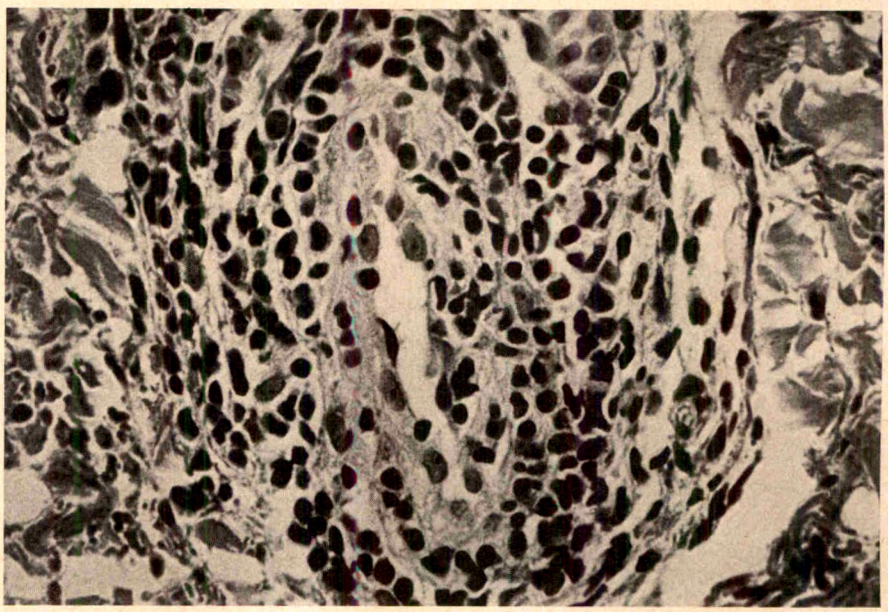

Fig 1.—Represents typical type IV delayed-type hypersensitivity cell-mediated immune response with perivascular lymphocytic infiltrate.

PPD (intermediate strength) skin tests for comparative purposes (Bacillus-Calumet-Guerin immunized). The normal controls were all healthy individuals known to the principal investigators and ranging in age from 4 to 38 years, whereas the patient population consisted of those individuals seen in the immunology clinic with suspected or proved immunodeficiency. They ranged in age from 17 months to 24 years (Table 1).

Diphtheria-TT, absorbed (pediatric DT) diluted 1:100 was used. In some cases, a dilution of 1:50 and 1:10 was used. An intradermal inoculation of 0.1 mL was injected and a wheal raised. Reactions were read at 30 minutes, and at 4 to 12, 24, 48, and 72 hours. Reactions were measured for the greatest diameter of erythema and induration with use of a clean, circular plastic millimeter ruler. All patients were matched for interval from vaccination to skin testing, and skin tested with the same lot of DT toxoid.

A 3-mm punch biopsy specimen was obtained under local anesthesia at the site of injection at 72 hours if any reaction at all had been seen during the previous observation period. Biopsy specimens were fixed in a 10% formaldehyde solution, stained with hematoxylin-eosin, and read by two independent observers (J.N. and W.M.) without any prior knowledge of the history or laboratory findings. The histologic criteria for a delayed hypersensitivity and for an Arthus-like reaction have been well described.[5,6] Briefly, a delayed hypersensitivity reaction is characterized by a dense mononuclear cell infiltrate (macrophages and lymphocytes) with occasional neutrophils and basophils, whereas the Arthus reaction is characterized by an acute inflammatory-type reaction with leukocyte clumping, platelet aggregates, and a noticeable neutrophilic accumulation (Fig 1 to 3).

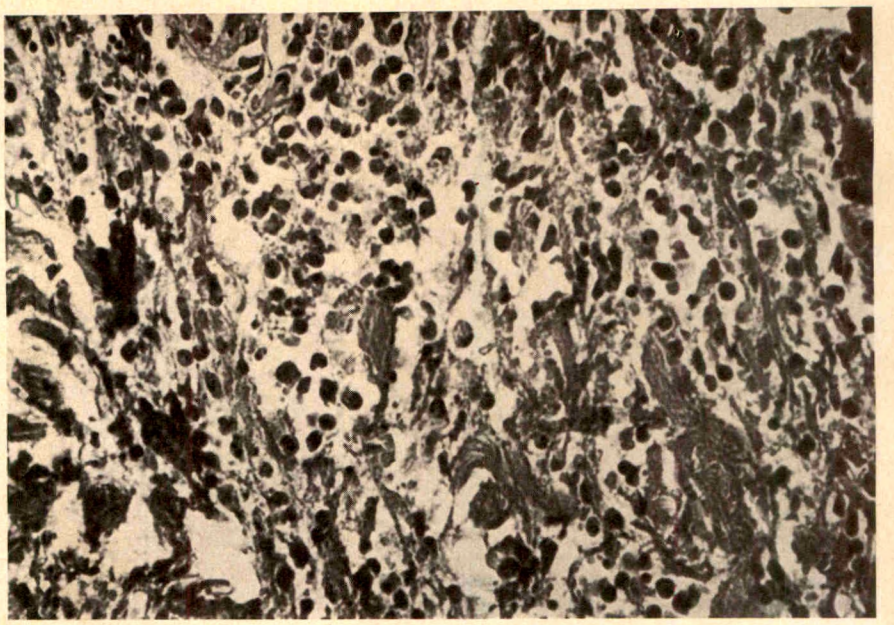

Fig 2.—Arthus-like reaction with acute necrotizing vesicular dermatitis associated with noticeable neutrophilic inflammatory response. Rare eosinophils and mononuclear cells are present.

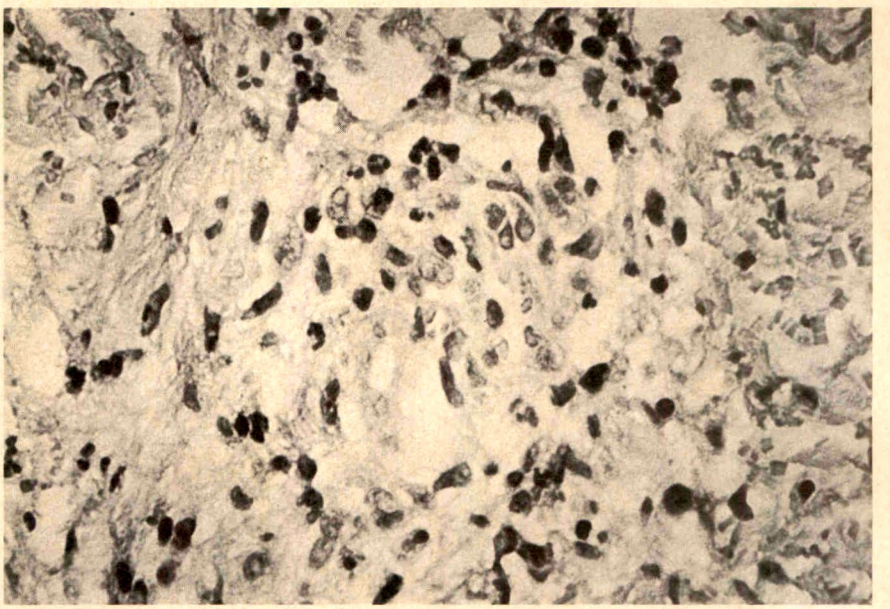

Fig 3.—Nonspecific inflammatory response with some features of both an Arthus and delayed-type hypersensitivity response. Infiltrate is predominantly neutrophilic with some perivascular response consisting of occasional lymphocytes, monocytes, and eosinophils.

RESULTS

The conditions of 13 subjects were completely evaluated. Of these, seven had some type of immune defect, including three with combined immunodeficiency. Reactions of 2 mm or less were difficult to measure accurately. Two patients did not undergo biopsy because no reaction was observed. The data from the visual observations are given in Table 1, whereas the histological data are given in Table 2.

If one uses the criterion of Pepys[7] (induration $\geq$ 10 mm at 48 hours) 2/6 or 33% of the normal controls were positive at 48 hours and one at 72 hours, whereas 2/7 or 29% of the patient group were positive at both 48 and 72 hours. If, however, one uses the criterion proposed by Franz et al[4] ($\geq$ 2 mm), 5/6 of controls were positive at 48 hours and 72 hours and 5/7 of the patients were positive at the same time. One normal control (skin test positive for monilia) and two patients (combined immunodeficiency [SCID]) had no reaction at all, with 1:100 dilution. For purposes of this article, positive skin tests to antigens other than DT were defined as induration greater than 5 mm at 48 hours and for DT greater than 2 mm.

Of the patients on whom biopsy was done, 3/6 (50%) demonstrated an Arthus-like reaction rather than de-

Table 2.—Histology of Skin Biopsy Specimens

Case	Remarks	Reaction
PPD controls		
1	...	Typical type IV hypersensitivity reaction with dense perivascular lymphocytic infiltrate admixed with occasional neutrophils
2	...	
Diphtheria-tetanus controls		
3	...	
4	...	
5	Few transformed lymphocytes (immunoblasts in perivascular infiltrate	
6	Fibrin deposits in dermal collagen	
8	...	
Patients		
9	Noticeable neutrophilic infiltrate	Moderate to severe perivascular dermal infiltrate suggestive more of Arthus reaction than cell-mediated response
10	Mild to moderate neutrophilic infiltrate	
11	Severe acute necrotizing perivascular infiltrate in dermis, with epidermal necrosis and vescicle formation	
12	...	Minimal perivascular lymphocytic infiltrate of the dermal vessels; response may not represent optimum cell-mediated response although consistent with type IV hypersensitivity reaction
13	...	
15	...	Moderate to severe perivascular dermal infiltrate suggestive more of nonspecific reaction than cell mediated response

layed hypersensitivity despite the fact that these three all had positive-appearing skin tests by observation and 2/3 were known to have combined immunodeficiency. Of the two other patients who underwent biopsy, the histologic reactions correlated poorly with the skin test readings despite the fact that both were considered positive (patients 12 and 13). Only one patient with SCID showed no reaction to the DT antigen. It is also interesting to note that three of the abnormal patient population had positive skin test reactions to streptokinase-streptodornase and/or monilia despite a questionable result in one and a negative result in the other two with the DT antigen (patients 13 and 14).

A dilution of 1:50 was used in four individuals, three controls and one abnormal (patient 15, Table 1) and were not different from the 1:100, other than a slight increase in erythema. Five subjects were tested with a dilution of 1:10. Two were nonimmune individuals who reacted with both erythema and induration immediately. Two were normal controls (patient 8, Table 1) who also showed positive results, and patient 15 who demonstrated a defective in vitro CMI had a nonspecific reaction at 1:10.

COMMENT

The value of delayed hypersensitivity testing for evaluation of cellular immune competence is generally considered to be established. The major clinical problem lies in the appropriate selection of antigens in the young child or infant. Monilia *(Candida albicans)* antigen, which has the greatest exposure rate, is an excellent antigen but still occurs in only 60% to 80% of the infants older than 7 months of age, and even all of these patients do not demonstrate positive skin test reactions.[8,9] The use of dinitrochlorobenzene poses problems in terms of required sensitization and the subsequent adverse responses, such as sloughing and scarring. The use of PHA as a skin test has proved useful to some investigators, but the correlation with in vitro studies has not been good and caution in the interpretation of both positive and negative results is necessary.[10]

The use of a specific antigen for skin testing would be extremely advantageous. With the routine use of DPT and measles, mumps, rubella vaccinations in children, an appropriate skin test antigen from one of these would be extremely valuable. Unfortunately, the use of mumps as an antigen has been of limited value because of the high degree of primary irritation and perhaps reactions to contaminating antigens.[11,12] Similarly, TT, which is advocated by some also shows a high degree of immediate and Arthus-type reactions and is, therefore, difficult to interpret.[3] Whether this phenomenon also relates to the reactions herein noted with DT is unknown at the present time. It would seem that TT does cause more reactions. Part of the problem may lie in the hyperimmunization that occurs with TT which, at least in the younger children, does not seem to be the case in our study. The question is raised if it would be better to develop an antigen for diphtheria skin testing that lacks tetanus. In this regard, Kuhns and Pappenheimer[13] reported a high incidence of immediate wheal and flare reactions to diphtheria toxoid in allergic as compared with nonallergic individuals.

Facktor et al[3] studied 70 normal individuals with TT, mostly in the older age group, and as noted previously, they demonstrated a high incidence of "reactions." However, biopsy specimens were taken in a few selected individuals to look for specific reactions. It is, therefore, difficult to compare their results either with those of Franz et al[4] or ourselves. Steele et al[9] demonstrated that tetanus was a better single screening antigen than monilia, the most often used single antigen. Similar studies with diphtheria alone have not been done. Thus, the issue has not been resolved, but at least theoretically diphtheria alone might be a better skin test antigen.

In this brief report, we have demonstrated that a high degree of irritant, immediate, and Arthus-type reactions do occur. Furthermore, there is a very

poor correlation between the histological results and the observed skin reactivity. A positive result at 48 or 72 hours, regardless of the criterion used for determining positivity, cannot safely be interpreted as reflecting CMI function. Some workers in the field have suggested the use of fluid TT often in the undiluted form. However, two points are worth mentioning. One is that fluid DT is no longer commercially available and, therefore, its value as a routine DTH test is restricted and it is often used at a concentration at least ten times greater than the 1:100 dilution in our study. In the study by Franz et al,[4] higher concentrations resulted in nonspecific reactions, particularly notable in that they occurred in unimmunized individuals.

We concur with their findings using less diluted antigen. Several patients tested with a 1:10 dilution comparable to the fluid DT had severe reactions, creating considerable discomfort to the patient. This also occurred in nonimmune individuals. Although the use of a 1:10 dilution may lead to more positive reactions it also increased the likelihood of adverse reactions and false-positive results.

We have no explanation as to why an Arthus-type reaction occurred only in suspected or proved immunodeficient patients. The lack of such reactions in the controls may be related to the numbers of patients evaluated or perhaps to a subtle defect in the complement activation pathway for C3 as has been proposed by Barandun et al[14] for reactions to immunoglobulins in immunodeficient patients.

We believe that if the DT toxoid delayed hypersensitivity skin test is to be used, it must be done in conjunction with a skin biopsy that, therefore, severely limits its usefulness as a screening test for disorders of immunity or inflammatory response. Thus, as a routine assay it is not recommended. It should also be noted that the standard criteria of 10 mm of induration used for assessing PPD reactions and other skin tests in adults is not applicable in children.

Our data would support the view shown by others, that since there does not seem to be any single antigen that is suitable for skin testing, multiple skin test antigens should be used for assessing delayed hypersensitivity responses. Our data would also support the view that the results of such testing be interpreted with caution and that, depending on the degree of clinical suspicion in any individual, more sophisticated tests, eg, lymphocyte stimulation, may be warranted to evaluate CMI.

The Michigan State Department of Public Health supplied the diphtheria-pertussis-tetanus material and did the measurement of diphtheria antibodies.

References

1. Sutherland D, Wilson S: Skin testing in the assessment of cell mediated immunity. *NZ Med J* 85:41-44, 1977.

2. Sokal J: Measurement of delayed skin test responses. *N Engl J Med* 293:501-502, 1975.

3. Facktor M, Bernstein R, Fireman P: Hypersensitivity to tetanus toxoid. *J Allergy Clin Immunol* 52:1-12, 1973.

4. Franz M, Carella J, Galant S: Cutaneous delayed hypersensitivity in a healthy pediatric population: Diagnostic value of diphtheria-tetanus toxoids. *J Pediatr* 88:975-977, 1976.

5. Udakak K: The Arthus reaction, in Movat HZ (ed): *Inflammation, Immunity and Hypersensitivity.* New York, Harper & Row, 1971, pp 390-423.

6. Vassalli P, McClusky R: Delayed hypersensitivity, in Movat HZ (ed): *Inflammation, Immunity and Hypersensitivity.* New York, Harper & Row, 1971, pp 180-234.

7. Pepys J: Skin tests in diagnosis, in Gell P, Coombs R (eds): *Clinical Aspects of Immunology.* Philadelphia, FA Davis, 1968, pp 189-220.

8. Shannon DC, Johnson G, Rosen F, et al: Cellular reactivity to *Candida albicans* antigen. *N Engl J Med* 275:690-693, 1966.

9. Steele R, Suttle D, LeMaster P, et al: Screening for cell mediated immunity in children. *Am J Dis Child* 130:1218-1221, 1976.

10. Bonforte R, Topilsky M, Siltzbach L, et al: Phytohemagglutinin skin tests: A possible in vivo measure of cell mediated immunity. *J Pediatr* 81:775-780, 1972.

11. Brunell P, Brickman A, O'Hare D, et al: Ineffectiveness of isolation of patients as a method of preventing the spread of mumps: Failure of mumps skin test antigens to predict immune states. *N Engl J Med* 279:1357-1361, 1968.

12. Horowitz S, Nagatini MS, Bowen GS, et al: The acquisition of delayed hypersensitivity following attenuated mumps virus infection. *Pediatrics* 45:77-82, 1970.

13. Kuhns WS, Pappenheimer AM: Immunochemical studies of antitoxins produced in normal and allergic individuals hyperimmunized with diphtheria toxoid. *J Exp Med* 95:363-374, 1952.

14. Barandun S, Skvaril F, Morell A: Prophylaxis and treatment of diseases by means of immunoglobulins. *Monogr Allergy* 9:39-60, 1975.

Editorial Life in the 14th Century

Multiple copying of manuscripts was no longer the monopoly of lonely monks in their cells but the occupation of professional scribes who had their own guilds. Licensed in Paris by the University, supposedly to ensure accurate texts, the scribes were the agony of living authors, who complained bitterly of the copyists' delays and errors. The "trouble and discouragement" a writer suffers, wailed Petrarch, was indescribable. Such was the "ignorance, laziness, and arrogance of these fellows" that when a writer has given them his work, he never knows what changes he will find in it when he gets it back.

BARBARA TUCHMAN (*A Distant Mirror*, New York, Alfred A Knopf Inc, p 453).

Circumcision and the Risk of Cancer of the Penis

A Life-Table Analysis

Mosze Kochen, MD, MPH, Stephen McCurdy, MPH

• The low incidence of penile cancer in the United States is frequently cited as a reason for not justifying the risk of neonatal circumcision as a prophylactic measure. Although uncircumcised men are uniquely at risk for this malignant neoplasm, previous approaches have used annual incidence data collected without regard to circumcision status, thus tending to underestimate the true risk to this susceptible group. In addition, the concept of lifetime risk has not been addressed. Using data from the Third National Cancer Survey and previously published circumcision prevalence figures in a life-table analysis, we estimated the lifetime risk for cancer of the penis in uncircumcised males. The predicted risk is 166 per 10^5, or one in 600; the estimated median age of occurrence is 67 years. These data deserve to be considered with other morbidity factors in the context of the neonatal circumcision debate.

(*Am J Dis Child* 134:484-486, 1980)

Circumcision, one of the most common surgical procedures on male subjects in the United States, continues to be controversial in terms of risks and benefits involved. Among the many points of debate is the protective value of the operation against cancer of the penis vs the morbidity of the procedure. The American Academy of Pediatrics states that circumcision is an effective method of preventing cancer of the penis.[1] It has been maintained, however, that in spite of this protective effect, the incidence of cancer of the penis is so low as not to justify the risks of circumcision.[2]

Incidence data for this malignancy are based on the number of cancers per year in 100,000 men, without regard to circumcision status. Since uncircumcised males are essentially the only population at risk, these figures underestimate the incidence of cancer of the penis in this uniquely susceptible group. In addition, annual incidence data do not address the lifetime risk for this cancer.

To contribute to the evaluation of neonatal circumcision from the standpoint of penile cancer prevention, we present an analysis of the lifetime risk of cancer of the penis in uncircumcised males.

SUBJECTS AND METHODS

Age-specific incidence rates for cancer of the penis in US males were obtained for the years 1969 to 1971 from the Third National Cancer Survey.[3] We assumed that virtually all of the reported cancers occurred in uncircumcised males. We therefore adjusted the rates for the estimated fraction of the population that was uncircumcised in each age group. Here we relied on circumcision prevalence values published in 1968 by Stern and Lachenbruch.[4] Their figures are based on physical examination of a nonrandom sample of 330 men. The fraction of uncircumcised men in each age group is given in Table 1, column 3.

Our adjusted age-specific rates were then applied to the US life table of 1971[5] for males of all races. This yielded the cumulative lifetime risk of cancer of the penis in uncircumcised males.

RESULTS

Table 1 summarizes the rate adjustment procedure and shows age-specific risk rates for cancer of the penis in uncircumcised men. These adjusted rates are applied to the 1971 US life

Table 1.—Adjustment of Age-Specific Incidence Rates for Cancer of the Penis

Age Group x_i-x_{i+n}, yr	Crude Incidence for Penile Cancer, 10^{-5} per Year*	Uncircumcised Fraction of Age Group[4]	Adjusted Risk Rate for Uncircumcised Men, 10^{-5} per Year
0-30	0.0	. . .	0.00
30-35	0.1	.39	0.26
35-40	0.4	.39	1.03
40-45	0.5	.50	1.00
45-50	0.9	.50	1.80
50-55	1.3	.54	2.41
55-60	2.6	.54	4.81
60-65	3.4	.56	6.07
65-70	5.4	.56	9.64
70-75	5.8	.45	12.89
75-80	4.9	.45	10.89
80-85	8.3	.45	18.44
85+	7.8	.45	17.33

*From Third National Cancer Survey.[3]

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table as given in Table 2. This yields a value of 166 per 10^5, or one in 600, as the cumulative lifetime risk for this malignant neoplasm; the predicted median age of occurrence is 67 years.

COMMENT

Penile Cancer

Cancer of the penis is rare in the United States (annual age-adjusted incidence 1.0 per 10^5 for 1969 to 1971).[3] The lifetime risk of having this condition was indirectly estimated. This analysis emphasizes incidence and does not specifically predict morbidity or mortality for those contracting the disease. At present, the major morbidity can be ascribed to the psychological and physical trauma of the disease and its therapy (usually surgery).

The median survival time for 67-year-old men (the predicted median age for getting penile cancer) is 7.5 years.[6] Life expectancy for unaffected men at this age is 12.1 years.[7] From this, one may roughly estimate 4.6 years of life lost per cancer, or more than 750 years per 10^5 uncircumcised men. To cause a comparable loss of years of life, circumcision would have to be responsible for approximately ten deaths per 10^5 neonates, assuming a life expectancy of 76 years at birth.

However, morbidity and mortality issues become at least as much philosophical as medical concerns. They are also subject to change owing to advancements in therapy and its availability to the patient. Therefore, we choose to focus chiefly on the incidence of the disease.

Comparison with the lifetime risks of other malignant neoplasms aids in providing perspective and allowing interpretation of our figures. A similar analysis using the same data sources yielded 225 per 10^5 as the lifetime risk for cancer of the testes, more than 1,500 per 10^5 for cervical cancer, and 4,800 per 10^5 for cancer of the prostate. Thus, for every lifetime incident of cancer of the penis, there are 1.4 cancers of the testes, nine of the cervix, and 29 of the prostate.

Two Basic Assumptions.—The accuracy of our estimate for lifetime penile cancer risk depends on the validity of two major assumptions. The first is that these cancers occur exclusively in uncircumcised males. This allows one to adjust population-based incidence rates for the fraction of the population that is uncircumcised and, therefore, the fraction at risk. The peculiar susceptibility of uncircumcised males to this malignant neoplasm is well known.[1] Leiter and Lefkovits,[8] in a review of the literature since 1936, found only nine reports of cancer of the penis in neonatally circumcised males.

The actual values of the adjusted age-specific risk rates depend partly on the estimates for frequency of circumcision taken from Stern and Lachenbruch.[4] We are aware of no other age-specific circumcision prevalence data for the United States that are based on physical examination. Although other sources of estimates are available, these data are unreliable[9] in that they are based solely on inquiry.

Stern and Lachenbruch's figures are based on a nonrandom sample of men and may not adequately represent the diverse socioeconomic makeup of the US population. Error owing to this sampling bias would probably not have a great effect on the final value for estimated lifetime risk. To illustrate, let us assume the figures from Leiter and Lefkovits[8] systematically overestimate circumcision rates by 50% across all ages. Compensating for this assumed bias reduces the lifetime risk for cancer of the penis by 25%, to 124 per 10^5. The incidence rates taken from the Third National Cancer Survey[3] are also subject to error. The most likely direction of bias is underestimation of the true incidence owing to incomplete reporting. These neoplasms in older men may not come to attention, especially if death intervenes from an unrelated cause not requiring autopsy.

The second major assumption on which this analysis is based concerns the validity of applying to the birth cohort of 1971 the age-specific risk rates derived from the experience of much older cohorts. To address this assumption, one must consider the secular trend of penile cancer incidence. The incidence of this malignant neoplasm has remained at a low level and exhibits a decline during the last three decades. In 1947, the age-adjusted risk of penile cancer was 1.4 per 10^5 per year [10]; in the period from 1969 to 1971, it was 0.9 per 10^5 per year.[3] Part of this decline may be explained by improved economic and living conditions. To the extent that this is the case, our analysis will overestimate the lifetime risk for those born in 1971.

The decline may be due in part to a cohort effect, however; ie, increased circumcision rates in younger cohorts would contribute to the overall lower-

Table 2.—Adjusted Age-Specific Risk Rates for Cancer of the Penis in Uncircumcised Males*

Age Group x_i-x_{i-n}, yr	No. Alive at Age x_i	Estimated No. Alive at Midpoint of Interval	Adjusted Penile Cancer Risk Rate for Uncircumcised Men, 10^{-5} per Year	Expected No. of Penile Cancers
0-30	100,000	97,036	0.00	0.00
30-35	94,072	93,535	0.26	1.22
35-40	92,997	92,269	1.03	4.75
40-45	91,541	90,455	1.00	4.52
45-50	89,369	87,720	1.80	7.89
50-55	86,070	83,605	2.41	10.07
55-60	81,139	77,549	4.81	18.65
60-65	73,958	69,138	6.07	20.98
65-70	64,318	58,307	9.64	28.10
70-75	52,296	45,547	12.89	29.35
75-80	38,797	31,859	10.89	17.35
80-85	24,921	19,045	18.44	17.56
85+	13,168	6,584	17.33	5.71
Total				**166.15**

*Rates applied to the 1971 US life table.[5]

ing of penile cancer incidence in the entire population. This latter effect would not affect our analysis since we exclusively address the risk to the uncircumcised male and not to the entire male population. We believe the life-table analysis provides a reasonable estimate of the risk for cancer of the penis in uncircumcised males.

Populations, Predictions, and Hygiene.—These figures largely reflect the experience of the white majority of the US population. The lifetime risk may be greater for racial groups with higher incidence rates and mortality for this malignant neoplasm. For instance, American blacks suffer a 2.5-fold increased annual incidence[3]; their mortality may be as much as four times higher than that of whites.[11] It is not clear what component of this increased risk may be accounted for by lower circumcision rates.

Since the uncircumcised male is uniquely susceptible, virtually all of these cancers are preventable by neonatal circumcision. The number of lifetime incident cancers that could be prevented annually by circumcision can be estimated with birth statistics available for 1971. In that year, there were 1,822,910 recorded live male births.[12] If none had been neonatally circumcised, our analysis predicts that one in 600, or more than 3,000 would have penile cancer in their lifetimes.

It has been suggested that careful penile hygiene could provide a level of protection nearly comparable with that provided by circumcision. St John-Hunt[13] and Diddle[14] have indicated, however, that adequate penile hygiene among uncircumcised males in Western countries is in fact not observed on a population basis.

Considerations Other Than Penile Cancer

A decision regarding the value of circumcision may not be made solely on the basis of penile cancer risk. Other points of consideration include the greater incidence of balanitis and phimosis in uncircumcised males as well as the risks of adult circumcisions these conditions may necessitate.[1] In addition, there is a finite complication rate for neonatal circumcisions. Frequency of important nonfatal complications (primarily hemorrhage, infection, and trauma) ranges from 0.06% to 0.25% in the three largest studies published since 1953[15-17]; these studies involved more than 24,000 patients. The rates may be expressed alternately as 60 per 10^5 and 250 per 10^5, respectively, and are comparable to the lifetime risk for penile cancer estimated here for uncircumcised males.

Mortality as a complication of circumcision is rare. A review of the literature since 1953 yielded only two reports of circumcision-related deaths.[15,18] *Vital Statistics for 1971*[7] records no male deaths in categories[19] that include not only circumcision-related deaths but also those owing to complications and misadventures of prophylactic appendectomies and sterilizations, among others. These figures may underestimate the true circumcision-related morbidity and mortality owing to reluctance on the part of physicians and hospitals to report such incidents. Difficulties in assigning cause of death where multiple medical problems contribute may also be a factor.

Finally, arguments based on religious and social preference continue to play a major role. Such issues are not amenable to the cost vs benefit approaches that can be applied to the more medical aspects. We submit that the lifetime risk for penile carcinoma deserves inclusion among these many factors figuring in the controversy regarding circumcision. Further investigation is indicated in several areas. Specifically, dependable data regarding circumcision rates and firm definition of related complications and their frequencies are needed. Comparable figures for disease usually attendant to the uncircumcised state (such as complications owing to phimosis and balanitis) would also be helpful. However, given the many fronts on which the subject is being debated, it is likely that circumcision will remain a controversial topic.

References

1. Thompson HC, King LR, Knox E, et al: Report of the Ad Hoc Task Force on Circumcision. *Pediatrics* 56:610-611, 1975.
2. Morgan WKC: The rape of the phallus. *JAMA* 193:123-124, 1965.
3. Cutler SJ, Young JL Jr (eds): *Third National Cancer Survey: Incidence Data*. National Cancer Institute Monograph 41. Bethesda, Md, US Dept of Health, Education, and Welfare, Public Health Service, 1975.
4. Stern E, Lachenbruch PA: Circumcision information in a cancer detection center population. *J Chron Dis* 21:117-124, 1968.
5. *National Life Tables: 1969-1971*, publication HRA 75-1150, vol 1, No. 1. Rockville, Md, US Dept of Health, Education, and Welfare, 1975.
6. Axtell LM, Asire AJ, Myers MH (eds): *Cancer Patient Survival: Report Number 5*, publication 77-992. Bethesda, Md, US Dept of Health, Education, and Welfare, National Institutes of Health, 1976.
7. *Vital Statistics of the United States, 1971*, Volume II: *Mortality*, Part A. Rockville, Md, US Dept of Health, Education, and Welfare, 1975.
8. Leiter E, Lefkovits AM: Circumcision and penile cancer. *NY State J Med* 75:1520-1522, 1975.
9. Lilienfeld AM, Graham S: Validity of determining circumcision status by questionnaire as related to epidemiological studies of cancer of the cervix. *J Natl Cancer Inst* 21:713-720, 1958.
10. Dorn HF, Cutler SJ: *Morbidity from Cancer in the United States*, Part 1, monograph No. 56. US Dept of Health, Education, and Welfare, Public Health Service, 1959.
11. Lilienfeld AM, Levin ML, Kessler II: *Cancer in the United States*. Cambridge, Harvard University Press, 1972, p 76.
12. *Vital Statistics of the United States*, 1971, Volume I: *Natality*. Rockville, Md, US Dept of Health, Education, and Welfare, 1975.
13. St John-Hunt D: Circumcision of the newborn: Is it good preventive medicine? *Med J Aust* 1:1100-1101, 1967.
14. Diddle AW: Should circumcision be done routinely? *Med Asp Hum Sex* 1:32-33, 1967.
15. Speert H: Circumcision of the newborn. *Obstet Gynecol* 2:164-172, 1953.
16. Shulman J, Ben-Hur N, Neuman Z: Surgical complications of circumcision. *Am J Dis Child* 107:149-154, 1964.
17. Gee WF, Ansell JS: Neonatal circumcision: A ten-year overview. *Pediatrics* 58:824-827, 1976.
18. Annunziato D, Goldblum LM: Staphylococcal scalded skin syndrome: A complication of circumcision. *Am J Dis Child* 132:1187-1188, 1978.
19. *Eighth Revision International Classification of Diseases (ICDA)*, vol 1. US Dept of Health, Education, and Welfare, Public Health Service, 1975, p 405.

Nonstandard Therapies in the Developmental Disabilities

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• The complexity of management issues with regard to developmentally disabled children has led to broad acceptance of a number of therapeutic approaches that purport to be effective for a wide range of problems. These are generally empiric in origin, and the efficacy of most of them cannot be supported by controlled research studies. In addition, there has been little or no investigation of potential or actual side effects. Acceptance of new therapies and validation of older approaches need to be based on appropriately designed, controlled studies.

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Developmentally disabled children present the professional therapist with a broad range of problems, including those of a cognitive, motor, behavioral, interpersonal, social, and familial nature. Because of the complexities involved in the development of management programs that will meet all of these needs, therapies purported to have a positive impact in all of these areas have great appeal. If they seem to be based on sound, scientific fact and if they seem to be free of obvious deleterious side effects, their acceptance is often rapid, complete, and uncritical.

Some of these therapies have become entrenched in clinical practice by many years of use. Generally, they have never been put to a critical, controlled trial. Other treatment methods are newer, and this article will review some of the most recent and most popular. This in no way implies endorsement of other treatments that are in common use but have never been adequately tested.

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NONSTANDARD THERAPIES

As stated earlier, there are "standard" therapies that never have been adequately evaluated. The meaning of "nonstandard" is ambiguous, but all of these methods share certain characteristics, which will be used to formulate an operational definition. (1) They all are said to be based on biochemical or neurophysiologic theories, but these theories are not congruent with current concepts of function of the CNS. (2) They all purport to be extremely effective in a broad range of developmentally disabled children; often, the diagnostic criteria are poorly defined. (3) They are said to be incapable of causing harm. (4) There have been no adequately controlled studies published in major peer-reviewed journals. Publication is typically in nonreviewed journals, books, or lay publications. Case material is anecdotal, and a testimonial approach is used. (5) The therapies often have an emotional appeal, and studies that do not confirm effectiveness are attacked defensively.

The specific treatment modalities to be discussed are the following: (1) biochemically based therapies: megavitamins, orthomolecular mineral therapy, additive-free diet, hypoglycemia; (2) neurophysiologically based therapies: patterning, optometric training.

BIOCHEMICALLY BASED THERAPIES

Megavitamins

This therapy is an attempt to treat dysfunction of the nervous system not due to specific vitamin deficiency with extremely large doses of a number of vitamins. The origin is in the work of Hoffer and Osmond,[1] who postulated that schizophrenia was due to the accumulation of toxic metabolites formed by abnormal body metabolism. In 1960, Hoffer et al[2] identified the putative toxin as an abnormal metabolite of epinephrine and developed a treatment protocol initially using niacin, and then also adding ascorbic acid and pyroxidine hydrochloride. A theoretical article by Pauling[3] in 1968 discussed these concepts and led to the coining of the term "orthomolecular psychiatry," which is often used as a synonym for megavitamin therapy.

The following year, Cott[4] published an article consisting of six case reports that suggested improvement of the conditions of children diagnosed as schizophrenic when treated with large doses of niacinamide, ascorbic acid, pyridoxine, vitamin E, and pantothenate calcium. He also implied that the great majority of the children were hypoglycemic. Further publications[5,6] extended these concepts to learning disabled children and to those with behavioral disorders. The nutritional concept was further broadened to raise questions of abnormalities in balance of mineral intake. Claims of lack of potential toxicity of this treatment are made in all of the reports. There has been little else published in support of these theories.

The theoretical basis for megavitamin therapy is open to question, as has been fully discussed by Herbert.[7] These vitamins, in the human organism, are essential to life by definition. They have no primary function, but are cofactors; that is, they combine with enzyme proteins and thus activate the function of the enzyme. This is adequately carried out at levels close to the recommended minimum daily allowances. An excess of vitamins has no additional effects once the sites are saturated, although addi-

tional apoenzyme may be produced. It has also been shown that huge doses of vitamins may cause very high levels in blood, but increase the levels within the CNS little or not at all.[8] Vitamin deficiences exist, but produce clearly defined and well-recognized clinical syndromes.

It is fair to ask whether the empiric findings show megavitamin therapy to be useful, even if the hypothesis on which the treatment is based is incorrect. Hoffer and co-workers' results have not been confirmed by large studies.[9,10] The clinical reports written by Cott and involving children[4,6] are difficult to interpret. Two make reference to 500 children who have been treated, without specific data being provided. The other provides six narrative case reports. Case material is described in such a way that diagnoses of specific children are not clear. None of the requirements of a properly performed drug study are met; that is, there is no clear definition of patients, measurements, or methods of evaluation. No double blind, placebo, or other techniques to remove the observor bias were used. They are, therefore, essentially anecdotal and testimonial statements, without interpretable data.

A double-blind, placebo-controlled study of megavitamins was carried out by Arnold et al[11] with 31 children who exhibited hyperkinetic behavior. After a two-week treatment period, changes in a number of rating scales were ascertained and a decision made as to whether response to treatment (unknown to the evaluator) was good enough to continue, or whether a change to another therapy was needed. The two children who responded well were both in the placebo group. Pretest-posttest ratings by parents and teachers failed to show any significant differences in children of either group.

The issue of the potential toxicity of this therapeutic technique is being seriously raised.[7,12-14] Vitamins fall into two major groups, fat-soluble (vitamins A, D, E, and K) and water-soluble (all of the others, including niacin, ascorbic acid, and pyridoxine). The fat-soluble vitamins are stored in the body and are only slowly excreted. Both vitamins A and D have well-known, seriously life-threatening side effects when taken in large doses, and generally are not included in megavitamin regimens, although there has been a case report of severe vitamin A poisoning in a 4-year-old boy who received this therapy.[15]

There is some question as to whether or not vitamin E actually is a vitamin. Side effects of large doses are many, and include headaches, nausea, fatique, dizziness, blurred vision, decreased sexual function, sores around the mouth, gastrointestinal disturbances, muscle weakness, hypoglycemia, and a clotting factor deficiency. It may antagonize the effects of vitamin A, and cause a relative deficiency of vitamin K. In most instances, vitamin K does not seem to be part of the therapeutic plan.

The water-soluble vitamins are not stored in the body, and large doses are very rapidly excreted and essentially wasted. However, massive doses can cause unpleasant and potentially dangerous side effects. Niacin (or niacinamide) has produced skin flushing, itching, circulatory disturbances, cramps, liver damage, elevated blood glucose levels, elevated uric acid levels with gouty arthritis, peptic ulcers, skin pigmentation, cardiac arrhythmias, and nervous panic. It also may produce a relative deficiency of pyroxidine. No definite toxicity of pyroxidine has been found, but there is some suggestion that it causes enlargement of the liver in experimental animals.

Large doses of ascorbic acid may precipitate gout, cause kidney stones, produce scurvy in the newborn infants of mothers who take large doses or in adults who suddenly stop large dosages, and cause abdominal cramps and diarrhea. It may interfere with urine tests for diabetes and test for blood in the stools. Large doses also may neutralize the effect of therapeutically administered anticoagulants, and cause the destruction of most of the vitamin B_{12} in the diet. There have been reports of breakdown of RBCs in people with glucose 6-phosphate dehydrogenase deficiency, and crises in patients with sickle cell disease.

Therapy With Minerals

A number of minerals are recognized as being important in human nutrition, including copper, zinc, magnesium, and manganese. They, as is true for the vitamins, do not function independently, but as cofactors in enzymes or other proteins. Because of the very small amounts needed to maintain health, they are usually considered to be trace elements. Balanced diets provide more than enough of all of these substances.

Little has been written about the possible role of these substances in developmental disabilities, although this was suggested by Cott.[5] Hair samples from learning disabled children and controls were analyzed for 14 elements by Pihl and Parkes.[16] Results of discriminant function analysis showed that the two groups could be separated at the 98% level of accuracy by using values for five elements. Levels of cadmium, manganese, and chromium were increased in the learning disabled children, whereas levels of cobalt and lithium were decreased. Although not used as discriminators, levels of lead and sodium were also increased. The authors pointed out that their definition of learning disability was overly general. It should also be noted that control samples were obtained 2½ months after the clinical samples and were, therefore, not analyzed simultaneously.

Except for this study, the majority of clinical reports have been anecdotal. A new therapy has arisen and the diagnosis of deficiency is usually based on the analysis of the mineral content of the patient's hair. Hair analysis has been used to detect certain types of heavy metal poisoning in forensic pathology, but the relationship between the hair's content of these substances and general mineral metabolism is unknown. In addition, there are many problems with hair analysis. These include the lack of standardized washing procedures and the need to group hair content norms by hair color, the condition of the hair (growing, resting, shed), and the portion of the hair analyzed.[17] A single hair may represent two or three years in the life of the patient and have very different mineral content in different areas of the shaft.

The use of this therapy is new and toxicity data are scanty. As a general principle, the body's mechanism for ridding itself of excess quantities of minerals is poor, and they tend to accumulate. Some, such as iron and

copper, have clearly defined, major toxic effects when ingested in excess. Zinc, a commonly used element in these therapies, was considered harmless, but has recently been reported to cause low levels of serum copper and abnormalities in both RBCs and WBCs.[18] It will be many years before the safety of the other minerals in these doses can be proved.

Additive-Free Diet

Feingold[19] published a book in 1975, in which he presented the hypothesis that hyperactivity and learning disabilities in children are due to natural salicylates in food and to certain food colorings and additives. The hypothesis states that hyperactivity is due to a nonimmunologic (nonallergic) response to these substances in children susceptible because of genetic variations. The mechanism involved the "innate releasing mechanism" of the brain. This theory has many problems. Which brain mechanism is implicated is unclear because the terminology is not standard, but Feingold possibly means the reticular activating system. Diagnostic criteria for hyperactivity and learning disability are not well defined, and the statement that these syndromes have increased in frequency in recent years is unsupported by any data. The genetic argument is not supported by data.

Assuming that the author made an accurate empiric observation despite the faulty hypothesis, it can be asked if properly designed clinical studies have confirmed the usefulness of this diet. An uncontrolled study of 15 children from Australia reported that ten parents were "quite certain" and three were "fairly certain" that the child improved on the diet and relapsed promptly with dietary infractions.[20]

The first controlled study was that of Conners et al.[21] A double-blind, crossover design that used a baseline diet, a control diet, and the additive-free diet was instituted with 15 children. The observers were teachers and parents who used standardized rating scales. When comparing the test diet with the child's baseline diet, both teachers and parents saw improvement and scored differences were at the $P < .05$ level of significance. Comparing the test diet with the control diet, teachers reported significant improvement, but parents did not. Although the test diet-control diet differences were significant, the mean scores represent only a small change in behavior. The author recommended a cautious approach in interpretation due to the small sample size and the inconsistent results.

A different approach was used by Williams et al.[22] Twenty-six children were organized into four groups based on administration of active (stimulant drugs) or placebo medications and of control cookies or challenge cookies that contained a number of food colorings. Results were determined by teacher and parent checklist ratings. Stimulant medications were clearly more effective than the diet in the reduction of hyperactivity; diet may have been of some slight use in from three to eight of the children, depending on the criteria used. Children receiving placebo possibly showed more activity with the challenge cookies than with the control cookies. The authors concluded that the diet may have use in certain children, but not as a general treatment.

Two other results of this study were of interest. The parents believed that the diet was effective when the children were also receiving medication, whereas the teachers found the diet to be the most effective in children not receiving stimulant drugs. The other finding that requires further study is that there was no exacerbation of hyperactivity after dietary lapses in those children who seemed to improve on the diet. For these reasons, the results are inconsistent but interesting enough to be pursued, and this may permit detection of a subgroup of responsive children.

The largest and most carefully designed study to date is that of Harley et al.[23] The investigators removed all food from the houses of the participating families, and supplied everything during the course of the study. All of the family members ate the experimental diets. Food was supplied for family guests and holidays, as well as to the entire class if any child in the room had a birthday. Several experimental and distracting procedures were used to obscure dietary changes. Observations included teacher ratings, objective classroom and laboratory observations, parental ratings, and psychological tests.

The results of this study provided no support for the hypothesis that the additive-free diet was effective. The parents who reported some improvement in the conditions of children on the diet only did so if the experimental diet followed the control diet. The reverse order showed no differences. Thirteen mothers rated their child's condition as improved on this diet sequence, whereas six mothers rated it as worse on the test diet. In no case did laboratory or classroom data confirm these findings. Interviews with the parents after the study showed that none could identify the sequence and timing of the diet crossovers used.

In a second phase of this study, the nine boys whose scores showed the best "response" and who were available to participate were placed on a strictly controlled, additive-free diet for 11 weeks.[24] Using a double-blind protocol, both placebo and additive-containing challenge foods were given with multiple crossovers. Measurements consisted of parental and teacher rating scales, classroom observation, and neuropsychological testing. The challenge with materials containing artificial color had no adverse effects. This does not support the hypothesis, and certainly does not support the concept that a dietary infraction rapidly causes a recurrence of abnormal behavior that can last for several days.

In summary, the well-controlled studies fail to document any improvement in the behavior of children on the additive-free diet. The positive results of uncontrolled studies can be ascribed to psychological factors.

The question of potential harm is obviously not as much of a concern as with the megavitamin and orthomolecular mineral approaches. Initial data showed borderline ascorbic acid levels in the diet, but this does not seem to be an important problem since salycylate-containing foods (many fruits and vegetables) are no longer restricted. There are four points that must be weighed in a cost-benefit analysis. The first is that the only successful way to assure implementation of the diet is to use it for the entire family. This change in

eating pattern and style may be unacceptable for other family members and lead to friction, focusing hostility on the patient. The second issue is that of the time, effort, and expense involved in trying to buy additive-free foods and in preparing foods that cannot be purchased without additives. If both parents are employed, the time commitments may be impossible to meet.

The third issue is that of the artificial and highly restricted nature of the diet and the inability of the child to join his peers for snacks, parties, or even regular meals. The developmentally disabled child has great difficulties with social interaction, peer group acceptance, and self-esteem. None of these are alleviated by the dietary restrictions. Finally, many of the medications that might be necessary for the child (anticonvulsants, antibiotics, antihistamines, etc) contain the forbidden substances. Resistance by the parents to giving drugs may develop and medical care compromised.

Hypoglycemia

The relationship between low blood glucose levels and learning disabilities was also suggested by Cott.[5] This has become a popular diagnosis for a host of neurologic and behavioral symptoms, with little or no documented, published experience. There are two important issues concealed within this "common" problem that is treated with such dietary strategies as low carbohydrate-high protein diets and frequent feedings. The first is that the diagnostic techniques are often improperly used. A proper glucose tolerance test requires adequate preparation of the patient with an appropriate diet before the glucose load is administered, a properly sized load, and blood specimens taken for at least five to seven hours. Correct interpretation of the laboratory results is obviously required, and the normal drop in blood glucose level should not be overinterpreted. The patient must show both a low blood glucose level and symptoms (pallor, diaphoresis, tachycardia) concurrently.

The most important fact is rarely discussed. If the patient is truly hypoglycemic, this is not necessarily a benign condition that should be treated with diet.[25] Careful evaluation and a number of metabolic tests are required to determine which of the many causes of hypoglycemia is involved. The conditions range from the annoying to the life-threatening. Some are genetic in origin and have implications for genetic counseling. Treatment ranges from surgery through drugs to diet. These evaluations are rarely if ever performed by those centers frequently using dietary treatment based on this diagnosis. The long-range effects of these diets on growth and development are not known.

NEUROPHYSICALLY BASED THERAPIES

Patterning

This is one of the most commonly applied and widely known of the neurophysiologic treatment techniques. The method, developed by Doman et al,[26] was based on theories of Temple Fay. The method attempts to move the abnormal brain through a normally sequenced developmental pattern by sensory stimulation and the imposition of passive movement on the patient. No well-controlled experimental studies were published, and the widespread popularity of the technique is based largely on testimonial evidence. The technique is time-consuming, and may require a large number of volunteer "therapists" to come to the child's house each day and assist with the patterning. The demands and time schedules are rigidly imposed, and failure to show developmental progress may be blamed on deviations from the routine.

In this treatment modality, the ideas of organization and reorganization of the CNS are inconsistent with current knowledge.[27] Twenty-five children, who ranged in age from 2 to 16 years and who suffered from a variety of neurologic conditions, were studied by Harel et al.[28] They were placed in a patterning program and followed up for 1½ years. At the end of this period of time, the parents were asked to give subjective evaluations of their child's progress. In nine of 20 cases, they believed that there had been "significant" improvement, and in another nine of 20, "some" improvement. Evaluation by standardized tests, however, showed great improvement in only one case, and some improvement in six. This clearly illustrates the problems with observer bias. In addition, there was no untreated control group. The authors pointed out that therapy required three to four hours per day for each child, and that eight families reported major stresses in family life around the issue of the heavy burden of the therapeutic program.

Sparrow and Ziegler[29] studied institutionalized, seriously retarded children. There were 15 subjects in each of three groups: patterning, motivational control, and no treatment. The study was continued for one year and there were a variety of outcome measures. All three groups showed some improvement in performance during the course of the study, but there was no difference in degree of improvement for the group that received patterning treatment, the group that received placebo treatment, and the group that received the usual treatments offered at the institution. The study thus failed to confirm any positive effect for the technique as applied to this group of children.

The potential harm of the method is not physical, but rather is its great expense and the investment of time by the parents and volunteers. This method may also hold out false hopes for the families and delay their ability to come to some accomodation with the severity of the child's deficit.

Optometric Training

The techniques subsumed under this term are many,[30] but are based on the theory that learning disabilities are primarily due to abnormal visual perceptual and sensory-motor coordination processes, and that they can be improved with various types of visual and neurologic organizational training. Two issues raised by this approach are important to examine. First, there is no evidence that reading disability involves the eyes, eye movement, or eye balance. Children with severe visual or oculomotor handicaps learn to read normally if the material is presented with appropriately sized type. The second issue is that current research is moving away from a perceptual abnormality model of dyslexia, and now emphasizes the areas of language disability, amnestic

syndromes, and more complex deficits in cognitive processing.[31] There is no reason to assume that ocular training will affect any of these abnormalities. Controlled data are virtually nonexistent.

As with patterning, the harm comes from the time and expense of a course of treatment with no proven benefit. In addition, it may distract the family from the key issue, that of appropriate special education.

COMMENT

The therapies discussed all attempt to offer specific, universally effective therapies for complex problems that are global and that vary from patient to patient. As indicated, controlled data are almost entirely lacking, and when present are equivocal. Risks range from increased expense and distraction from more important issues, to potentially severe physical harm.

When faced with the task of evaluating a new therapy, a fairly standard approach can be used. The first question to be asked is whether the theory on which the therapy is based is consistent with current concepts of the anatomy, physiology, and biochemistry of the CNS. Then, there must be a cost-benefit analysis that balances the evidence that the treatment is effective against the potential, recognized or theoretical, for harm.

Effectiveness should only be accepted if based on properly designed studies. This requires the same rigorous approach as would be built into any laboratory study, and the design should include appropriate controls, adequate measurement techniques, and a large, clearly defined, and fully described experimental group. It should always be remembered that the burden of proof is on the proponents of the treatment. They must prove efficacy. Critics of the technique need not prove noneffectiveness, but should insist on positive data from the proponents.

The question of the ethics of denying the treatment to the control group in studies is often raised. In fact, it is unethical in most instances not to carry out the controlled study. Not only may it fail to show a therapeutic effect, it is always possible that it may show the treatment to be harmful or worse than no treatment at all. The history of medicine is full of such examples.

It should never be assumed that any treatment is harmless. This is, of course, true of biochemical treatments, but also true of behavioral therapies. Patients must be followed up for a long period of time to search for delayed problems. Also, for this reason, short-term studies cannot be used to justify long-term treatment. The lack of signs of toxicity of a drug given over a three-week period does not in any way prove that it will be harmless if given for months or years. This is of particular concern with the use of massive doses of vitamins and minerals.

The cost-benefit analysis must also take into consideration monetary strains on the family, time commitment, and the effect of these on the other family members. The effect of the therapy on the child's ability to function in peer group settings outside of the therapy situation cannot be neglected. Treatment must never be allowed to distract from the core issues of special education, social growth, individual adjustment, and family interactions.

The scientific approach to scientific problems cannot be replaced by untested hypotheses leading to undocumented therapies. Bronowski[32] stated that, "Magic is a technology, technology without science." Each person must decide whether to practice science or magic.

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References

1. Hoffer A, Osmond H: *The Chemical Bases of Clinical Psychiatry.* Springfield, Ill, Charles C Thomas Publisher, 1978.

2. Hoffer A, Osmond H, Smythies J: Schizophrenia: A new approach: II. Results of a year's research. *J Ment Sci* 100:29-54, 1954.

3. Pauling L: Orthomolecular psychiatry. *Science* 160:265-271, 1968.

4. Cott A: Treating schizophrenic children. *Schizophrenia* 1:44-60, 1969.

5. Cott A: Orthomolecular approach to the treatment of learning disabilities. *Schizophrenia* 3:95-105, 1971.

6. Cott A: Megavitamins: The orthomolecular approach to behavioral disorders and learning disabilities. *Acad Ther* 7:245-258, 1972.

7. Herbert V: Megavitamin therapy. *J Am Pharmaceutical Assoc* 17:764-766, 1977.

8. Spector R: Vitamin homeostasis in the central nervous system. *N Engl J Med* 296:1393-1398, 1977.

9. Ban TA, Lehmann ME: Nicotinic acid in the treatment of schizophrenias: Canadian Mental Health Association Collaborative Study Progress Report II. *Can Psychiatr Assoc J* 20:103-112, 1975.

10. Task Force Report: *Megavitamins and Orthomolecular Therapy in Psychiatry.* Washington, DC, American Psychiatric Association, 1973.

11. Arnold LE, Christopher J, Huestis RD, et al: Megavitamins for minimal brain dysfunction. *JAMA* 240:2642-2643, 1978.

12. Herbert V: Facts and fictions about megavitamin therapy. *Resident Staff Physician* 24:43-50, 1978.

13. National Nutrition Consortium: *Report of the Committee on Safety, Toxicity, and Misuse of Vitamins and Trace Minerals.* Chicago, American Dietetic Association, 1978.

14. Rechcigl M (ed): *CRC Handbook Series in Nutrition and Food: Nutritional Disorders.* West Palm Beach, Fla, CRC Press Inc, 1978, vol 1.

15. Shaywitz BA, Siegel NJ, Pearson HA: Megavitamins for minimal brain dysfunction: A potentially dangerous therapy. *JAMA* 238:1749-1750, 1977.

16. Pihl RO, Parkes M: Hair element content in learning disabled children. *Science* 198:204-206, 1977.

17. Lazar P: Hair analysis: What does it tell us? *JAMA* 229:1908-1909, 1974.

18. Prasad AS, Brewer GJ, Schoomaker EB, et al: Hypocupremia induced by zinc therapy in adults. *JAMA* 240:2166-2168, 1978.

19. Feingold B: *Why Your Child Is Hyperactive.* New York, Random House, 1975.

20. Cook PS, Woodhill JM: The Feingold dietary treatment of the hyperkinetic syndrome. *Med J Aust* 2:85-90, 1976.

21. Conners CK, Goyette CM, Southwick DA, et al: Food additives and hyperkinesis: A controlled double-blind experiment. *Pediatrics* 58:154-166, 1976.

22. Williams JI, Cram DM, Tausig FT, et al: Relative effects of drugs and diet on hyperactive behaviors: An experimental study. *Pediatrics* 61:811-817, 1978.

23. Harley JP, Matthews CG, Eichman P: Synthetic food colors and hyperactivity in children: A double-blind challenge experiment. *Pediatrics* 62:975-983, 1978.

24. Harley JP, Ray RS, Tomasi L, et al: Hyperkinesis and food additives: Testing the Feingold hypothesis. *Pediatrics* 61:818-828, 1978.

25. Pagliara AS: Hypoglycemia, in Rudolph AM (ed): *Pediatrics,* ed 16. New York, Appleton-Century-Crofts, 1977, pp 716-729.

26. Doman RJ, Spitz EB, Zucman E, et al: Children with severe brain injuries: Neurologic organization in terms of mobility. *JAMA* 174:257-262, 1966.

27. Cohen MJ, Birch HG, Taft LT: Some considerations for evaluating the Doman-Delacato "patterning" method. *Pediatrics* 45:302-314, 1970.

28. Harel H, Shapiro Y, Spirer Z: A follow-up study of children with neurodevelopmental disabilities treated by the Delacato team, abstracted. Read before the 6th National Meeting of the Child Neurology Society, Charlottesville Va, Oct 6, 1977.

29. Sparrow S, Ziegler E: Evaluation of a patterning treatment for retarded children. *Pediatrics* 62:137-150, 1978.

30. Silver LB: Acceptable and controversial approaches to treating the child with learning disabilities. *Pediatrics* 55:406-415, 1975.

31. Mattis S, French JH, Rapin I: Dyslexia in children and young adults: Three independent neuropsychological syndromes. *Dev Med Child Neurol* 17:150-163, 1975.

32. Bronowski J: *Magic, Science, and Civilization.* New York, Columbia University Press, 1978.

CSF Neurotransmitter Studies

An Infant With Ascorbic Acid-Responsive Tyrosinemia

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• A female newborn infant with Marfan-like habitus experienced lethargy and hypothermia associated with tyrosinemia that was not corrected by the administration of ascorbic acid at 50 mg/day but that subsequently responded to ascorbic acid at 500 mg/day. Cerebrospinal fluid analysis for neurotransmitter metabolites showed elevated concentrations of homovanillic acid and 5-hydroxyindoleacetic acid when the child was symptomatic and normal concentrations after successful ascorbic acid therapy. These observations suggest that a high level of tyrosine in serum can affect the metabolism in the brain of dopamine and serotonin.

(*Am J Dis Child* 134:492-494, 1980)

Transient neonatal tyrosinemia (serum tyrosine level > 4 mg/dL) is a common finding in premature infants. A high-protein diet, decreased activity of the enzyme parahydroxyphenylpyruvic acid oxidase, and a low ascorbic acid intake lead to transient impairment in the oxidation of tyrosine.[1] The administration of low doses of ascorbic acid orally or parenterally can abolish the tyrosinemia.[2] Decreased motor activity, lethargy, and poor feeding have been associated with elevated tyrosine levels.[3,4] Several follow-up studies have indicated that neurological and intellectual development are normal in children who had neonatal tyrosinemia.[5-7] However, Mamunes et al[8] have described intellectual deficits in full-term infants with transient neonatal tyrosinemia.

This report describes a premature infant with phenotypic features of Marfan's syndrome who had hypothermia, lethargy, and poor feeding associated with an elevated serum tyrosine level that was unaltered by the recommended dose of ascorbic acid but that responded to large doses of ascorbic acid. Cerebrospinal fluid neurotransmitter metabolite concentrations were abnormal during the period of symptomatic tyrosinemia, but they returned to within normal limits when serum tyrosine concentrations became normal. The CSF neurotransmitter metabolite findings in this individual patient with transient tyrosinemia are important considerations in the unresolved question of the potential harmfulness of transient tyrosinemia.

REPORT OF A CASE

This female patient weighed 1,940 g at birth, an appropriate weight for her gestational age of 35 weeks. The Apgar scores were 6 at one minute and 7 at five minutes. Her parents were a 20-year-old, gravida 2, para 1, abortus 1 mother, and a 21-year-old, nonconsanguineous father, both of whom had negative family histories for features of Marfan's syndrome. Physical examination of the infant disclosed plagiocephaly, long and thin extremities, an arm span 3.6-cm greater than her length, arachnodactyly, slender feet with flexed toes, and mild pectus excavatum. Her ophthalmologic examination showed no abnormalities. She had no evidence of congenital heart disease. A chest roentgenogram showed 11 pairs of ribs and tapered clavicles. The infant's immediate postnatal course was complicated by hyperbilirubinemia caused by A-O blood group incompatibility and sepsis that was suspected but not confirmed when she became hypothermic and tachypneic.

Urine tests to rule out homocystinuria revealed a positive nitrosonaphthol test at 2 weeks of age. Chromatographic analysis of amino acids in her serum detected a mildly elevated tyrosine level of 4.9 mg/dL during the third postnatal week (Table 1). Prolonged neonatal tyrosinemia was suspected at age 7 weeks when her serum tyrosine level increased to 12.9 mg/dL although her diet contained less than 4 g of protein per kilogram per day. A trial of oral ascorbic acid, 50 mg/day, for four days was given with no substantial change in the serum tyrosine level. The potency of the ascorbic acid was not tested. At age 10 weeks, she had gastroenteritis that was treated with clear liquids, and her serum tyrosine level declined to 2.9 mg/dL.

At 12 weeks of age, after resuming a regular diet for age without vitamin supplementation, she had poor feeding, hypothermia, and lethargy. Blood, urine, and CSF cultures obtained to evaluate suspected bacterial sepsis were sterile. The serum tyrosine concentration was 18.0 to 23.9 mg/dL, and the serum phenylalanine concentration was 3.3 mg/dL. A lumbar puncture was performed to obtain CSF for analysis of neurotransmitter metabolites.

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The serum tyrosine level decreased sharply after cessation of oral feedings and the institution of intravenous (IV) fluid therapy. An oral diet containing less than 5 g of protein per kilogram per day was started; simultaneously, the patient was treated with ascorbic acid, 500 mg/day, orally for one week. The serum tyrosine concentration decreased to 6.6 mg/dL and subsequently remained less than 5 mg/dL when she was receiving a regular diet without supplemental ascorbic acid. At 15 months of age, when the patient's diet was normal, concentrations of serum amino acids and CSF neurotransmitter metabolites were again analyzed.

No further episode of lethargy or hypothermia has occurred. She has continued to demonstrate Marfan-like features with neither ophthalmologic nor cardiac abnormality, and she has had mild hip contractures. Her growth was appropriate for the first 2 years; during her third year, she exhibited greater than normal increases in height and arm span. Her psychomotor development was normal at 1 year of age, as assessed by the Denver Developmental Screening Test and the Gesell Developmental Schedule. At age 26 months, her speech was delayed; but by age 3 years, her speech was developing normally.

LABORATORY METHODS

In the two samples of CSF obtained from the lumbar subarachnoid space of the patient and in CSF samples from 16 control subjects, homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methyoxy-4-hydroxyphenylethylene glycol (MHPG) were measured by a quantitative gas chromatographic-mass spectrometric method.[9] The CSF for HVA, 5-HIAA, and MHPG measurements was collected in glass tubes containing 2 mg/mL of ascorbic acid, was placed on ice, and was stored at −80 °C. Control subjects were children of similar age to the subject when studied who had lumbar punctures for investigation of neurological problems including cerebral palsy, psychomotor retardation, and neuromuscular and myoclonic disorders. Concentrations of amino acids in serum were analyzed by automated ion-exchange chromatography.[10]

RESULTS OF NEUROTRANSMITTER METABOLITE STUDIES

The basal levels of HVA and 5-HIAA seemed substantially elevated when the child was lethargic and hypothermic, and the serum tyrosine level was elevated. A year later, tyrosine concentration was normal in the serum, CSF concentrations of HVA and 5-HIAA had decreased to normal, and the MHPG value was normal (Table 2).

Table 1.—Serum Tyrosine and Phenylalanine Concentrations*

Age, wk	Tyrosine, mg/dL	Phenylalanine, mg/dL	Comments
2	3.8	1.4	. . .
3	4.9	. . .	. . .
5	11.8	2.8	. . .
7	12.9	2.5	. . .
8	10.7	2.3	After ascorbic acid, 50 mg/day for 4 days
10	2.9	. . .	Clear liquid diet
12	18.0	3.3	Regular diet; poor feeding, hypothermia, lethargy
	23.9	. . .	First CSF neurotransmitter studies
	8.6	. . .	Nothing by mouth; intravenous fluids
13	6.6	. . .	During ascorbic acid, 500 mg/day, and 5 g/kg/day protein diet
14	5.0	. . .	After ascorbic acid, 500 mg/day for 7 days
20	4.0	3.0	No ascorbic acid supplementation; regular diet
36	2.7	. . .	. . .
60	2.3	2.3	Repeated CSF neurotransmitter studies
112	3.8	1.4	. . .

*In preterm patient with tyrosinemia.

Table 2.—Biogenic Amine Metabolites in CSF

Metabolite	Age of Subject, 3 mo	Age of Controls, 1-10 mo	Age of Subject, 15 mo	Age of Controls, 11-24 mo
Homovanillic acid, ng/mL	371	117 ± 50* (8)†	134	129 ± 27 (8)
5-hydroxyindoleacetic acid, ng/mL	128	40 ± 18 (8)	52	49 ± 22 (8)
3-methoxy-4-hydroxyphenylethylene glycol, ng/mL	ND‡	16 ± 7 (8)	16	11 ± 3 (7)

*Mean ± SD.
†Number in parentheses indicates number of control patients.
‡ND indicates not determined.

COMMENT

Three aspects of this infant's course are especially noteworthy: (1) her abnormal phenotype, (2) the response to larger-than-usual doses of ascorbic acid, and (3) the CSF neurotransmitter studies. In premature infants, the maximum serum tyrosine level usually occurs by the third week of life; concentrations then spontaneously return to normal by the sixth week.[1,11] Although ascorbic acid deficiency has not been demonstrated, administration of ascorbic acid at 50 to 100 mg/day usually corrects the disorder if the protein intake does not exceed 5 g/kg/day. In this patient, the administration of much larger doses of ascorbic acid were associated with resolution of the tyrosinemia after usual doses had failed. Although the serum tyrosine concentration had declined to 8.6 mg/dL while the patient was maintained on IV dextrose infusion prior to the start of ascorbic acid therapy at 500 mg/day, there was no return to high serum tyrosine values with the resumption of oral protein intake as had occurred during the 12th week when ascorbic acid was not given.

The clinical symptoms of sepsis and CNS depression in neonates with tyrosinemia have been described but not understood. Although the inhibition of

myelination has been shown in newborn rats with tyrosinemia,[12] the effect of tyrosine on the developing human nervous system is unknown. The role of abnormal levels of neurotransmitters or their metabolites in the brain in the presence of elevated serum amino acids is particularly intriguing.

The aromatic amino acid tyrosine is a precursor in the biosynthesis of the catecholamine neurotransmitters dopamine, norepinephrine, and epinephrine.[13] Systemic administration of tyrosine to rats for short periods will increase brain levels of tyrosine and 3, 4-dihydroxyphenylalanine (DOPA), the immediate precursor of dopamine.[14] Systemic administration of levodopa for short periods to mice will increase dopamine, have no effect on norepinephrine, and decrease serotonin levels in the brain.[15] Levodopa administered systemically to rats will transiently increase brain levels and accelerate turnover of norepinephrine.[16] In rat-brain slices, levodopa is converted to dopamine, which displaces serotonin from neurons,[17] an observation that supports other evidence that systemic administration of levodopa will deplete brain serotonin reserves.[18]

The basal levels of HVA and 5-HIAA in the lumbar CSF reflect the biosynthesis, storage, and degradation in the brain of dopamine and serotonin, respectively.[19] Levels in the CSF of MHPG, the main metabolite of norepinephrine, are believed to indicate brain levels of that neurotransmitter.[20] The HVA and 5-HIAA values in the CSF from this patient obtained on two occasions suggest that a high level of tyrosine in serum can affect the metabolism of dopamine and serotonin and potentially norepinephrine. Unnatural amino acids, as precursors of false neurotransmitters, affect normal neurotransmitter metabolism in the brain.[21] In addition, the natural precursor amino acids in abnormal concentrations will affect normal neurotransmitter biosynthesis.[22] The elevated levels of HVA and 5-HIAA in the CSF could indicate extremely high levels of these acidic metabolites in the brain, which could directly and adversely affect brain function.[23]

The above experimental data indicate that tyrosine increases brain dopamine levels and HVA production and that serotonin, displaced from neurons by excess dopamine, is then further degraded to 5-HIAA. Although this would be consistent with our results, there could be other explanations for these changes in CSF metabolites, such as an increased degradation of both neurotransmitters. On the first occasion that the CSF neurotransmitter metabolites were measured, the child had received ascorbic acid four weeks previously. Thus, another possible explanation for the increase in CSF metabolites of dopamine and serotonin could be the stimulation by L-ascorbate of the hydroxylation of the aromatic amino acids tyrosine and tryptophan at the rate-limiting step in dopamine and serotonin biosynthesis.[24] However, this in vitro effect was not seen in rat brain in which ascorbic acid caused an increase in norepinephrine but a decrease of dopamine in areas of the brain.[25] The importance of the results, however, is to indicate the potential role of a perturbation of catecholamine and indoleamine neurotransmitters in the developing brain because of an elevation of tyrosine in the serum. Whether abnormal concentrations of neurotransmitter metabolites are present in the CSF from patients with other forms of tyrosinemia unassociated with Marfan-like habitus is presently not known.

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Nonproprietary Name and Trademarks of Drug

Levodopa—*Bendopa, Dopar, Larodopa.*

References

1. Avery ME, Clow CL, Menkes JH, et al: Transient tyrosinemia of the newborn: Dietary and clinical aspects. *Pediatrics* 39:378-384, 1967.
2. Levine SZ, Marples E, Gordon HH: A defect in the metabolism of aromatic amino acids in premature infants: The role of vitamin C. *Science* 90:620-621, 1939.
3. Scriver C, Clow C, Ramos A, et al: Tyrosinemia: Common, harmful, remediable, abstracted. *Can Med Assoc J* 94:673, 1966.
4. Partington MW, Campbell D, Kuyek J, et al: Motor activity in early life: III. Premature babies with neonatal tyrosinaemia: A pilot study. *Biol Neonate* 18:121-128, 1971.
5. Light IJ, Sutherland JM, Berry HK: Clinical significance of tyrosinemia of prematurity. *Am J Dis Child* 125:243-247, 1973.
6. Martin HP, Fischer HL, Martin DS, et al: The development of children with transient neonatal tyrosinemia. *J Pediatr* 84:212-216, 1974.
7. Menkes JH, Chernick V, Ringel B: Effect of elevated blood tyrosine on subsequent intellectual development of premature infants. *J Pediatr* 69:583-588, 1966.
8. Mamunes P, Prince PE, Thornton NH, et al: Intellectual deficits after transient tyrosinemia in the term neonate. *Pediatrics* 57:675-680, 1976.
9. Swahn C-G, Sandgärde B, Wiesel F-A, et al: Simultaneous determination of the three major monoamine metabolites in brain tissue and body fluids by a mass fragmentographic method. *Psychopharmacol* 48:147-152, 1976.
10. Brown JH, Walker S, Casto L, et al: Computerized data analysis of amino acids in physiologic fluids. *J Chromatogr* 116:293-304, 1976.
11. Mathews J, Partington MW: The plasma tyrosine levels of premature babies. *Arch Dis Child* 39:371-378, 1964.
12. Chase HP, O'Brien D: Effect of excess phenylalanine and of other amino acids on brain development in the infant rat. *Pediatr Res* 4:96-102, 1970.
13. Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology*, ed 2. New York, Oxford University Press, 1974, pp 90-201.
14. Wurtman RJ, Larin F, Mostafapour S, et al: Brain catechol synthesis: Control by brain tyrosine concentration. *Science* 185:183-184, 1974.
15. Everett BM, Bocherding JW: L-DOPA: effect on concentrations of dopamine, norepinephrine, serotonin in brains of mice. *Science* 168:849-850, 1970.
16. Chalmers JP, Baldessarini RJ, Wurtman RJ: Effects of L-DOPA on norepinephrine metabolism in the brain. *Proc Nat Acad Sci* 68:662-666, 1971.
17. Ng KY, Chase TN, Colburn RW, et al: L-DOPA-induced release of cerebral monoamines. *Science* 170:76-77, 1970.
18. Bartholini G, DaPrada M, Pletscher A: Decrease of cerebral 5-hydroxytryptamine by 3,4-dihydroxyphenylalanine after inhibition of extracerebral decarboxylase. *J Pharm Pharmacol* 20:228-229, 1968.
19. Moir ATB, Ashcroft GW, Crawford TBB, et al: Cerebral metabolites in cerebrospinal fluid as a biochemical approach to the brain. *Brain* 93:357-368, 1970.
20. Chase TN, Gordon EK, Ng LKY: Norepinephrine metabolism in the central nervous system of man: Studies using 3-methoxy-4-hydroxyphenylethylene glycol levels in cerebrospinal fluid. *J Neurochem* 21:581-587, 1973.
21. Kopin IJ: Unnatural amino acids as precursors of false transmitters. *Fed Proc* 30:904-907, 1971.
22. Daniel PM, Moorhouse SR, Pratt OE: Amino acid precursors of monoamine neurotransmitters and some factors influencing their supply to the brain. *Psychol Med* 6:277-286, 1976.
23. Giardina WJ, Sabelli HC: Evidence for the biological activity of the deaminated metabolites of the adrenergic amines. *Biol Psychiatry* 9:11-23, 1974.
24. Stone KJ, Townsley BH: The effect of *L*-ascorbate on catecholamine biosynthesis. *Biochem J* 131:611-613, 1973.
25. Izquierdo JA, Jofre IJ, Acevedo C: The effect of ascorbic acid on the cerebral and adrenal catecholamine content in the male rat. *J Pharm Pharmacol* 20:210-214, 1968.

Acute Caffeine Overdose in the Neonate

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• **To our knowledge, the clinical course of acute caffeine poisoning in neonates has not been previously reported. Three full-term infants manifested CNS irritability after the parenteral administration of large doses of caffeine and benzoate sodium injection in the delivery room for respiratory depression. The infants received caffeine in doses that ranged from 36 to 136 mg/kg. On arrival in a regional newborn center, they exhibited one or more of the following symptoms: tachypnea, fine tremor of the extremities, opisthotonus, tonic-clonic movements, and nonpurposeful jaw and lip movements. The overdose of caffeine produced a clinical picture that suggested neonatal seizures and prompted therapy with anticonvulsants. A fourth infant (premature) attained a high plasma caffeine concentration, but this infant's symptoms were altered by intraventricular hemorrhage. The combination of caffeine overdose and perinatal asphyxia may precipitate or increase seizure activity in the neonate. Recognition of the potential toxic effects of caffeine overdose should guide patient care and stimulate further study to establish appropriate use of caffeine in the newborn infant.**

(*Am J Dis Child* 134:495-498, 1980)

Although acute caffeine poisoning in adults has been reported since 1883,[1] the effects of caffeine overdose in newborn infants are apparently unrecorded in the medical literature. Caffeine and other methylxanthines, such as theophylline and theobromine, have many effects, including diuresis, smooth muscle relaxation, skeletal muscle stimulation, myocardial stimulation, and CNS stimulation. The stimulation of the medullary respiratory center increases the rate and depth of respiration and sensitizes this center to carbon dioxide.[2] This effect has been exploited in the treatment of apnea of prematurity. Both theophylline and caffeine are useful in the management of recurrent episodes of apnea, when underlying pathology has been excluded.[3,4]

Neonatal exposure to caffeine occurs as a result of maternal transmission through breast milk[5] and from therapeutic use in the delivery room or nursery. Even though the use of caffeine in the delivery-room management of apnea seems limited and controversial, a contemporary textbook of neonatology[6] states that caffeine is "well tolerated . . . [and] large doses may be given without serious ill effects."

We studied four neonatal cases of caffeine poisoning after administration of an injectable preparation of caffeine. After the diagnosis of caffeine poisoning in the index patient, three additional cases were discovered during a three-week surveillance of admissions to the local newborn center. Plasma caffeine concentrations were measured in three patients with a previously described high pressure liquid chromatographic assay adapted for caffeine.[7]

REPORT OF CASES

Case 1.—The patient was a 2,660-g, full-term girl born to an 18-year-old primagravida. The pregnancy was uneventful and labor was spontaneous. Delivery was complicated by cephalopelvic disproportion. A low-forceps delivery was unsuccessfully attempted, so the infant was delivered spontaneously. At birth, the Apgar score at 1 minute of age was 5 and the infant required vigorous physical stimulation and oropharyngeal suction. An intramuscular injection of 94 mg/kg of caffeine was

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given as a solution of caffeine and benzoate sodium. The Apgar score at 5 minutes of age was 10. The child had no difficulty until 18 hours of age, when "arching of the back" developed. Dexamethasone and phenobarbital were given intramuscularly. She remained opisthotonic for 12 hours and so was transferred to the University of Tennessee Newborn Center, Memphis.

On admission to the Center, her temperature was 38.2 °C; pulse rate, 180 beats per minute; respirations, 68/min; and systolic blood pressure, 110 mm Hg. The infant was hypertonic, with opisthotonic posturing and clenched fists, and had coarse tremors of all extremities. She was awake, crying, and extremely irritable. Arterial blood examination on admission showed a pH of 7.46; P_{CO_2}, 13 mm Hg; and P_{O_2}, 44 mm Hg. In addition, the hematocrit value was 62.5%; hemoglobin, 20.2 g/dL; WBCs, 17.9 × 10^3/cu mm, with 1% band forms, 73% neutrophils, 17% lymphocytes, 8% monocytes, and 1% myelocytes. The serum calcium concentration was 9.9 mg/dL; sodium level, 145 mEq/L; potassium level, 3.7 mEq/L, and glucose oxidase paper strip test, 90 mg/dL. A lumbar puncture at that time was traumatic. Cultures of the blood and CSF were made and therapy with ampicillin sodium and gentamicin sulfate begun. Ultimately, all cultures showed no growth. The baby's opisthotonic posturing persisted through the next day despite therapy with sodium bicarbonate and intravenous (IV) diazepam. She was given nasogastric feedings, a small amount of IV fluids, and chloral hydrate for her persistent tremors. At age 5 days, the infant's condition had begun to improve, but she still had minimal opisthotonic posturing; her plasma caffeine concentration was 31.9 μg/mL. At 7 days of age, the patient was asymptomatic and the caffeine concentration was 10.4 μg/mL. A repeat lumbar puncture showed ten WBCs, which were 100% mononuclear, 116 RBCs, a protein concentration of 75 mg/dL, and a glucose concentration of 53 mg/dL. An EEG and computerized tomographic (CT) scan of the brain were normal. The child was discharged after two weeks with no seizure activity.

Case 2.—The patient was a 3,760-g full-term infant born to a 20-year-old gravida 2, para 1. The pregnancy was complicated by diabetes mellitus without prenatal care. In addition, the mother had preeclampsia during labor. Maternal medications given during delivery included magnesium sulfate, furosemide, hydralazine, chlorothiazide, and reserpine. Information about the delivery was not complete, but it was a difficult, low-forceps delivery with a nuchal cord. The Apgar score at 1 minute of age was 0. The baby received 68 mg/kg of caffeine as caffeine with benzoate sodium by umbilical vein catheter while in the delivery room. At 2 hours of age, the baby became lethargic and appeared to be in mild respiratory distress. While receiving oxygen, he was given 4 mg of dexamethasone, 0.11 mg of atropine, and another dose of caffeine (68 mg/kg), all intramuscularly. Subsequently, the infant was transferred to the University of Tennessee Newborn Center.

On arrival, his temperature was 37.4 °C; pulse rate, 180 beats per minute; respiratory rate, 82/min; and systolic blood pressure, 74 mm Hg. The infant was jittery and hyperirritable, with posturing of the extremities and purposeless movements of the mouth. Results of admission arterial blood measurements gave a pH of 7.28, P_{CO_2} of 36 mm Hg, and P_{O_2} of 39 mm Hg while receiving 94% oxygen. The WBCs were 36.0 × 10^3/cu mm, with 23% band forms, 25% neutrophils, 32% lymphocytes, 10% monocytes, 2% eosinophils, and 6% metamyelocytes. The serum calcium concentration was 8.5 mg/dL; sodium concentration, 138 mEq/L; potassium concentration, 3.8 mEq/L; and glucose oxidase paper strip test, 90 mg/dL. The CSF had RBCs, 2,830/cu mm, and WBCs, 40/cu mm, 60% as mononuclear forms, a total protein concentration of 87 mg/dL, and a glucose concentration of 68 mg/dL. Gram stains and cultures of the CSF and blood ultimately showed no growth. Shortly after admission, the infant was treated with 2 mg/kg of IV tolazoline hydrochloride. Arterial blood values immediately improved to a pH of 7.49, P_{CO_2} of 24 mm Hg, and P_{O_2} of 144 mm Hg. During the next 24 hours, the pH remained elevated with a decreased P_{CO_2}, but improving oxygenation allowed the infant to be placed in room air. The symptoms of hyperirritability persisted. These were considered to represent seizure activity and were managed with administration of phenobarbital and intermittent administration of diazepam. The irritability continued for three additional days. Thereafter, the symptoms gradually diminished and caffeine poisoning was suspected. During this period of improvement, further studies showed a normal CT scan of the brain and a normal EEG. The patient was discharged and followed up as an outpa-

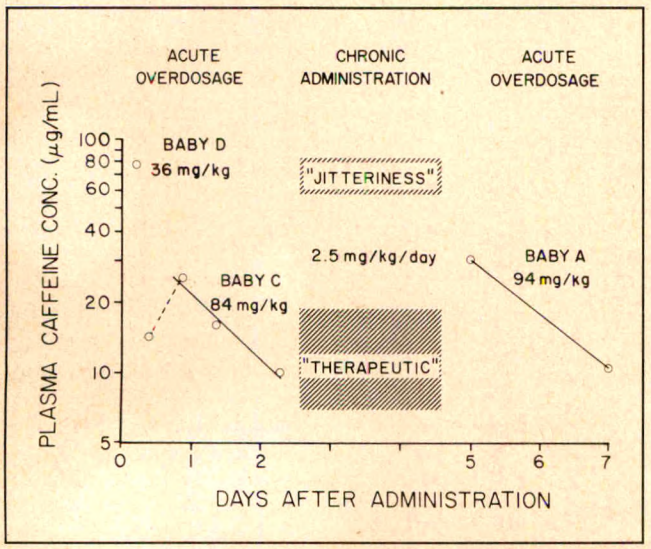

Fig 1.—Comparison of plasma caffeine concentrations in neonates (cases 1, 3, and 4) in whom severe toxicity developed after an acute overdosage, and those who experienced mild toxicity after long-term administration in pharmacokinetic study.[8]

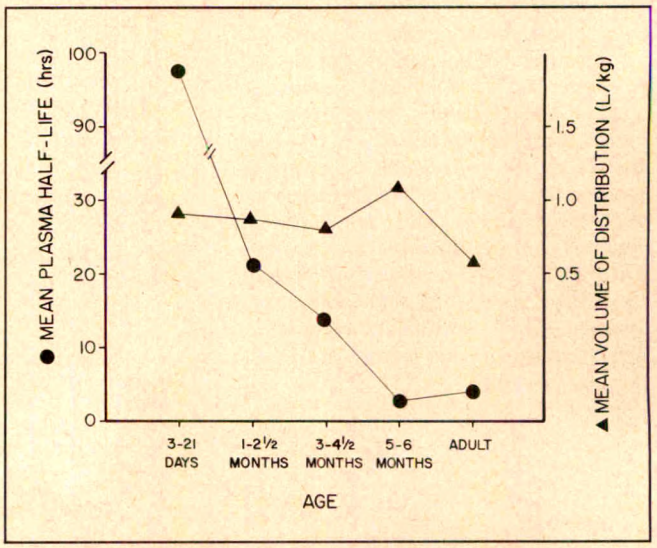

Fig 2.—Comparison of pharmacokinetics of caffeine in infants[15] and adults.[16]

tient. Plasma caffeine concentrations were not determined since this was the index patient. Three months after discharge, the child did not exhibit any further seizure activity and was doing well.

Case 3.—The patient was a 2,960-g, full-term infant born to a 21-year-old primagravida. The presentation was frank breech, but a vaginal delivery was performed. The delivery of the infant's head was delayed for ten minutes and a nuchal cord was noted. The mother received a total of 75 mg of IV meperidine hydrochloride prior to delivery. After delivery, the baby had a normal pulse rate, but had no spontaneous respiration. He was intubated, ventilated, and given an unknown dose of naloxone hydrochloride intramuscularly and 84 mg/kg of caffeine as caffeine with benzoate sodium intramuscularly. Thereafter, the infant began to have spontaneous respirations and was subsequently transferred to the University of Tennessee Newborn Center.

On admission, the temperature was less than 34.4 °C, the pulse rate was 104 beats per minute, the respiratory rate was 48/min, and the systolic blood pressure was 88 mm Hg. Neurologic examination showed upward deviation of both eyes and alternating periods of hypertonicity and hypotonicity. Results of arterial blood examination were as follows: pH, 7.24; Pco_2, 26 mm Hg; Po_2, 120 mm Hg. The serum calcium concentration was 9.0 mg/dL; sodium concentration, 142 mEq/L; potassium concentration, 5.4 mEq/L; and glucose oxidase paper strip test, 90 mg/dL. The infant was given IV fluids and phenobarbital. Plasma caffeine concentrations were determined at 8.5, 20.0, 32.5 and 57.5 hours of age and were reported as 13.7, 26.1, 16.7, and 10 μg/mL, respectively (Fig 1). Additional evaluation included a normal CSF analysis results and a normal CT scan. The infant continued to have rigidity, tonic movements, and purposeless lip movements for four days. The patient was discharged after ten days of therapy with phenobarbital (5 mg/kg/day). There was no further evidence of seizure activity.

Case 4.—The patient was a 1,730-g infant born to a 32-year-old gravida 3, abortus 1, at 32 weeks' gestation. She was delivered by cesarean section for a breech presentation and partial abruption. Apgar scores were 2 and 4 at age 1 and 5 minutes, respectively. The infant required oxygen by mask and was given 0.5 mL of caffeine with benzoate sodium (36 mg of caffeine per kilogram) intramuscularly. She was then transferred to the University of Tennessee Newborn Center for evaluation and management.

On admission, the infant was bradycardic and hypotensive, with severe acidosis and almost no respiratory effort. She was resuscitated with a good response initially. At 5 hours of age, the plasma caffeine concentration was 79.9 μg/mL. At 12 hours of age, the baby's vital signs suddenly deteriorated. A clinical diagnosis of intracranial hemorrhage was made, which was later confirmed by CT scan. The infant received volume expanders and packed RBCs. She required ventilatory support for two weeks and exhibited seizure activity for four days. Ultimately, the infant survived, with severe neurologic sequelae. No other caffeine determinations were obtained because it was believed that the large amount of plasma and blood given the infant would alter the caffeine concentrations.

COMMENT

The newborns described here were given caffeine doses that ranged from 36 to 136 mg/kg. All doses greatly exceeded the 10 mg/kg loading dose of caffeine suggested by Aranda et al[8] for the treatment of recurrent neonatal apnea. Assuming a cupful of coffee to contain 100 mg of caffeine, 25 to 95 cups of coffee would provide to an adult (70 kg) the amount of caffeine comparable to the acute overdose in these infants.

It is difficult to distinguish clearly the contribution of perinatal hypoxia to the symptoms of caffeine overdose. Central nervous system irritability after perinatal hypoxia is typically manifest by tonic posturing or clonus of one or more of the extremities; eyelid blinking, nystagmus, or ocular deviation; orofacial grimacing or automatisms; autonomic dysfunction; and apnea.[9] Information on the manifestations of caffeine poisoning is derived from the few case reports of acute poisoning in children and adults. Bren et al[10] reported a 7-week-old infant with tonic posturing, fixed upward gaze, and irritability after the ingestion of strong tea. Sullivan[11] reported a case of caffeine poisoning in a 12-month-old child who had "coffee ground" emesis, tachycardia, agitation, twitching of the extremities, hyperglycemia, ketonuria, and hypertension. These symptoms, which were associated with a serum caffeine concentration of 46 μg/mL, occurred nine hours after an ingestion of an unknown amount of caffeine in the form of 100-mg tablets (No-Doz). Similar symptoms were observed in a 3-year-old child who ingested 78 mg/kg of caffeine also in tablet form.[12] We are aware of a 2-year-old boy who was treated at our institution and survived a massive ingestion of a combination of extracts of buchu, uva ursi, triticum, and zea, and caffeine (Tri-Aqua; caffeine, 92 mg/tablet). The child's symptoms consisted of hematemesis, tachycardia (170 beats per minute), and coarse muscle fasciculations of the extremities and abdomen, with alternating states of stupor and hyperirritability. He achieved a peak plasma concentration of caffeine of 190 μg/mL at 12 hours postingestion. Furthermore, the symptoms of our first three cases were compared to those reported in older infants and children, as follows: neonates showed hyperirritability, opisthotonus, hypertonicity alternating with hypotonicity, upward ocular deviation, rigidity, and purposeless lip movements; whereas, the older children showed hyperirritability, tonic posturing, stupor alternating with agitation, upward ocular deviation, muscle fasiculations, hypertension, tachycardia, hyperglycemia/ketonuria, and emesis/hematemesis. Symptoms of CNS irritability occurred in both groups. However, the hypertension, hyperglycemia, ketonuria, and hematemesis that occurred in children were not apparent in our younger patients. The symptoms observed in our patients may not have been exclusively due to caffeine poisoning; however, the caffeine would probably exacerbate any previous irritability and confuse the clinical presentation.

Adverse effects of neonatal caffeine therapy were noted in a pharmacokinetic study in which transient jitteriness developed in three newborn infants with plasma caffeine concentrations of 58.4 to 84 μg/mL.[8] Case 4 had concentrations in this range, but two of our babies exhibited serious symptoms at much lower concentrations (Fig 1). A review of four adult fatalities[13,14] associated with caffeine overdosage shows a wide range of postmortem blood caffeine concentrations (1,040.0, 158.5, 106.0, and 79.0 μg/mL). This discrepancy may reflect

differences between short-term vs long-term exposure or interpatient sensitivity to the toxic effects of caffeine. It is possible that there is a predisposition to caffeine-induced toxicity in asphyxiated neonates.

Particular care should be taken in administering caffeine to newborn infants because the elimination of caffeine is greatly impaired in neonates.[15] In fact, the rate of elimination of caffeine does not approach the rate observed in adults until the age of 5 to 6 months (Fig 2). Therefore, caffeine administered to neonates is likely to result in prolonged effects, when compared with children and adults. Another consideration with the use of injectable caffeine with benzoate sodium is the potential risk of bilirubin displacement by benzoate sodium.[17] The use of injectable diazepam in the neonate is generally avoided because it contains benzoate sodium 50 mg/mL; whereas, the injectable caffeine preparation used in these cases contains benzoate sodium 125 mg/mL.

The four cases reported here demonstrate that large doses of caffeine are not universally well tolerated by newborn infants and may be potentially dangerous. We suggest that caffeine be reserved for the infant with recurrent apnea when infectious, metabolic, and neurologic causes have been excluded. This precludes its use during the immediate postpartum period. When caffeine is indicated for recurrent apnea, the dosage and therapy should be monitored and evaluated by measurement of plasma caffeine concentrations, as described by Aranda et al.[8] In this way, the toxicity of a potentially useful drug may be avoided.

Between the presentation and publication of this article, a similar case was reported in *Pediatrics* (64:254, 1979).

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Sheldon B. Korones, MD, and the staff of the University of Tennessee Newborn Center gave assistance. James F. Beattie, MD, and John F. Williams, MD, brought the index patient to our attention.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection.*

Caffeine—*Brite, Cafamil, Cafecon, Nodaca, No-Doz.*

Gentamicin sulfate—*Garamycin.*

References

1. Routh CHF: Case of poisoning by citrate of caffeine; recovery. *Lancet* 1:680-681, 1883.

2. Ritchie JM: Central nervous system stimulants: The xanthines, in Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co Inc, 1975, pp 367-378.

3. Kattwinkel J: Neonatal apnea: Pathogenesis and therapy. *J Pediatr* 90:342-347, 1977.

4. Aranda JV, Garman W, Bergsteinsson H, et al: Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. *J Pediatr* 90:467-472, 1977.

5. Breast feeding and drugs in human milk. *Vet Human Toxicol* 20:346-375, 1978.

6. Cohen H, Moya F, Lehr D: Drug therapy, in Abramson H (ed): *Resuscitation of the Newborn Infant*, ed 3. St Louis, CV Mosby Co, 1973, pp 178-179.

7. Maijub AG, Stafford DT, Chamberlain RT: Theophylline and dyphylline levels in serum by liquid chromatography. *J Chromat Sci* 14:521-525, 1976.

8. Aranda JV, Cook CE, Gorman W, et al: Pharmacokinetic profile of caffeine in the premature newborn with apnea. *J Pediatr* 94:663-668, 1979.

9. Vannucci RC: Neurologic aspects of perinatal asphyxia. *Pediatr Ann* 7:802-812, 1978.

10. Bren AS, Martin H, Stern L: Toxicity from tea ingestion in an infant: A computer simulation analysis. *Clin Biochem* 10:148-150, 1977.

11. Sullivan JL: Caffeine poisoning in an infant. *J Pediatr* 90:1022-1023, 1977.

12. Rowland D, Mace J: Caffeine (No-Doz) poisoning in childhood. *West J Med* 124:52-53, 1976.

13. DiMaio VJM, Garriott JC: Lethal caffeine poisoning in a child. *Forensic Sci* 3:275-278, 1974.

14. Turner JE, Cravey RH: A fatal ingestion of caffeine. *Clin Toxicol* 10:341-344, 1977.

15. Aranda JV, Collinge JM, Zinman R, et al: Maturation of caffeine disposition in infancy, abstracted. *Clin Res* 25:674A, 1977.

16. Axeland J, Reichenthal J: The fate of caffeine in man and a method for its estimation in biological material. *J Pharm Exp Ther* 107:519-523, 1952.

17. Schiff D, Chan G, Stern L: Fixed drug combinations and the displacement of bilirubin from albumin. *Pediatrics* 48:139-141, 1971.

Newborn Screening in New York State

In 1964 New York State implemented a PKU (phenylketonuria) Screening Program for all newborns. In 1974 additional conditions were added to the screening program, as listed below.

Since the inception of the screening program, the following number of children have been identified as having these conditions:

	No.	Incidence
PKU	215	1:16,700
Galactosemia	24	1:73,000
Branched chain ketonuria	2	1:600,000
Histidenemia	6	1:160,000
Homocystinuria	2	1:480,000
Adenosine deaminase deficiency	1	1:1,200,000
Sickle cell disease	158	1:4,300

As of December 1, 1978, congenital hypothyroidism was added to the mandated screening program. The expected incidence of congenital hypothyroidism is about 1:4,400.

New York State Department of Health (September 1979).

Falsely Normal Radionuclide Scans for Osteomyelitis

Gary R. Fleisher, MD; Jan E. Paradise, MD; Stanley A. Plotkin, MD; Spencer Borden IV, MD

• Three children are described with osteomyelitis confirmed by roentgenogram, blood culture, bone culture, and/or histologic findings. None had an abnormal technetium scintigram. Despite the lack of falsely normal bone scans for osteomyelitis reported in the literature, our cases demonstrate the importance of instituting antibiotic therapy on the basis of clinical suspicion since no single nonsurgical procedure can be relied on to make a diagnosis of osteomyelitis.

(*Am J Dis Child* 134:499-502, 1980)

In childhood osteomyelitis, prompt institution of therapy can increase the likelihood of complete recovery. However, early diagnosis may be difficult since laboratory tests and roentgenograms frequently do not distinguish osteomyelitis from cellulitis, septic arthritis, toxic synovitis, or trauma. The ESR and WBC count may be normal and, if elevated, are not specific for bone infection. In a series by Dich et al,[1] culture of the blood yielded an organism in only 57% of the patients with subsequently proved osteomyelitis. Capitanio and Kirkpatrick[2] observed soft-tissue changes early in the course of some cases of childhood osteomyelitis, but roentgenograms are often normal until seven to ten days after the initial visit.

Recent attention has focused on the scintigraphic detection of osteomyelitis in children. It has been stated that scintigraphy can establish the diagnosis of osteomyelitis soon after the onset of symptoms and before roentgenographic changes become apparent.[3-8] Although radionuclide scanning has also been a useful technique for this purpose at our hospital, we recently encountered three children with osteomyelitis who had normal bone scans early in the course of their illness. This report emphasizes the importance of instituting antibiotic therapy on the basis of clinical suspicion since no single nonsurgical procedure can be relied on to make a diagnosis of osteomyelitis.

REPORT OF CASES

Case 1.—A 12-year-old boy was admitted to the Children's Hospital of Philadelphia for evaluation of left hip pain of two days' duration. He appeared mildly ill, and his temperature was 39.2 °C. Palpation of the abdomen elicited mild, diffuse tenderness, but there was no rebound tenderness, mass, or organomegaly. Bowel sounds were normally active. The area of the left hip and sacroiliac joint was tender without erythema, warmth, or edema. Internal and external rotations of the left hip were limited by pain. The remainder of the physical examination showed no abnormalities.

Laboratory studies disclosed the following values: hemoglobin, 9.8 g/dL; hematocrit, 30%; and WBC count, 10,400/cu mm, with 81% neutrophils, 16% lymphocytes, and 3% monocytes. The ESR (Wintrobe) was 60 mm at one hour, and electrophoresis indicated hemoglobin A. Results of urinalysis were normal. Roentgenograms of the chest, left hip, sacroiliac joint, and lumbosacral area of the spine showed no lytic lesions or periosteal elevation.

Aspiration of the left hip joint yielded 0.5 mL of clear synovial fluid, with 60 WBCs per cu mm, and no bacteria were seen on Gram's stain. The initial therapy for a presumed osteomyelitis was nafcillin sodium. The initial blood culture and a repeated blood culture 24 hours later had growths of *Staphylococcus aureus*, which were sensitive to nafcillin. The joint culture and all subsequent blood cultures were sterile.

A radionuclide scan using technetium Tc 99m pyrophosphate (Fig 1, left) was normal on the second hospital day, and a repeated bone scan and roentgenograms were normal on the fifth hospital day. An intravenous pyelogram showed an extrinsic compression of the bladder on the left side, and a film of a barium enema showed a mass that impinged on the sigmoid colon. These findings were interpreted as consistent with retroperitoneal lymph node enlargement.

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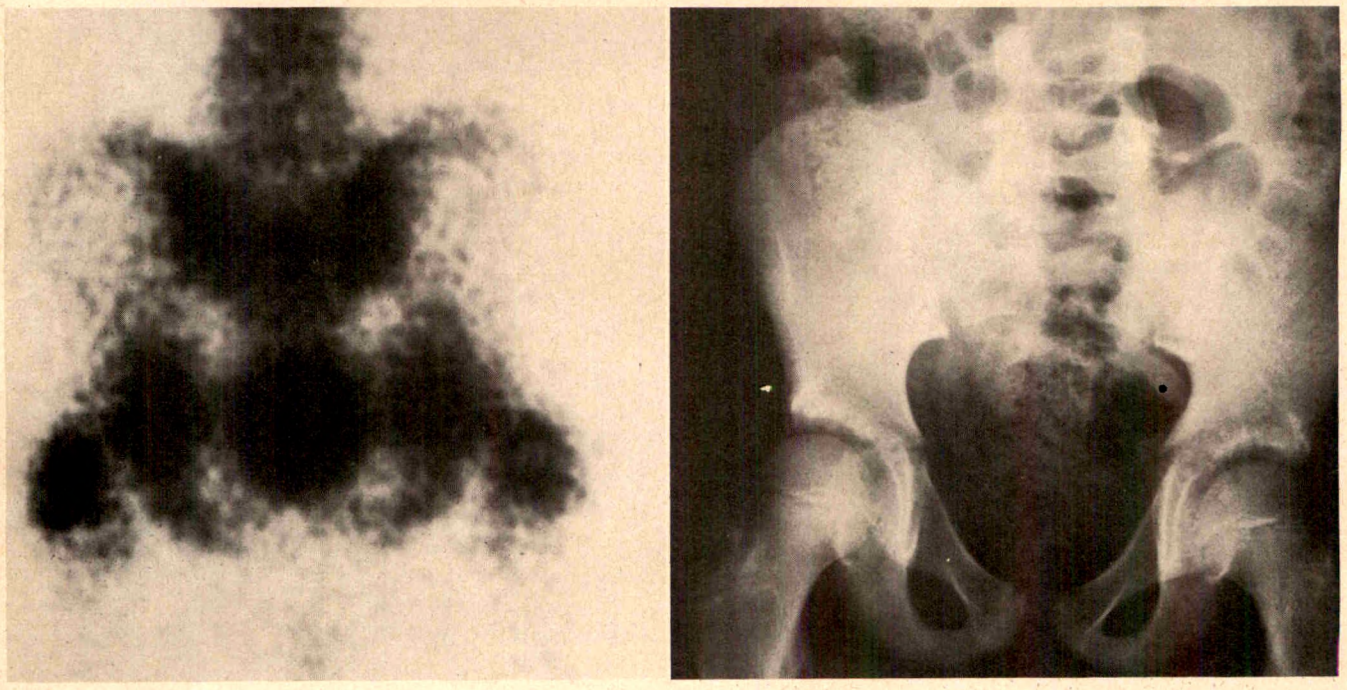


Fig 1.—Case 1. Left, Normal bone scintigram. Right, Roentgenogram on 17th hospital day, showing lytic lesion in ilium adjacent to left sacroiliac joint.

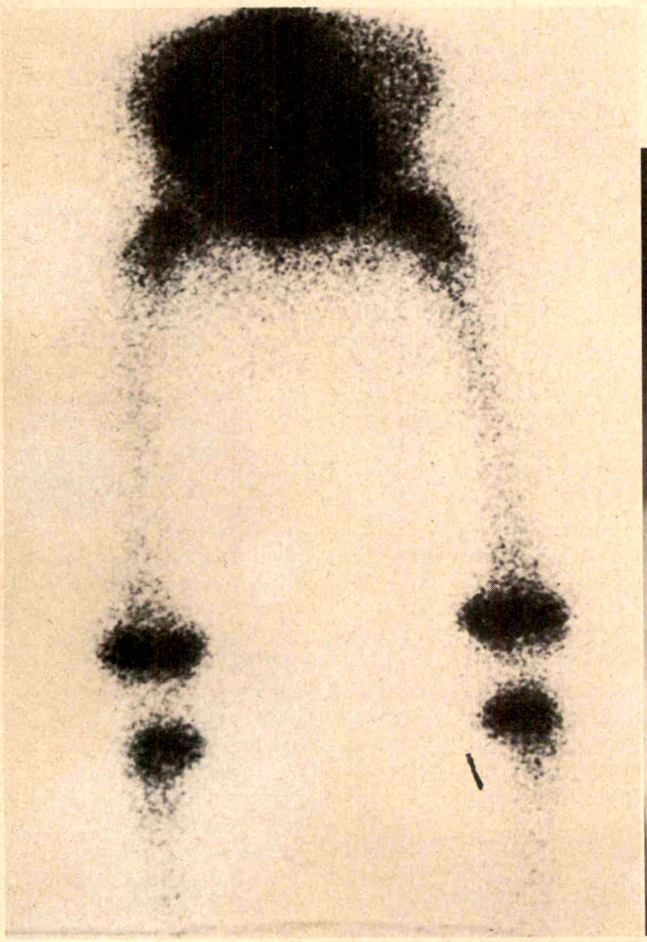
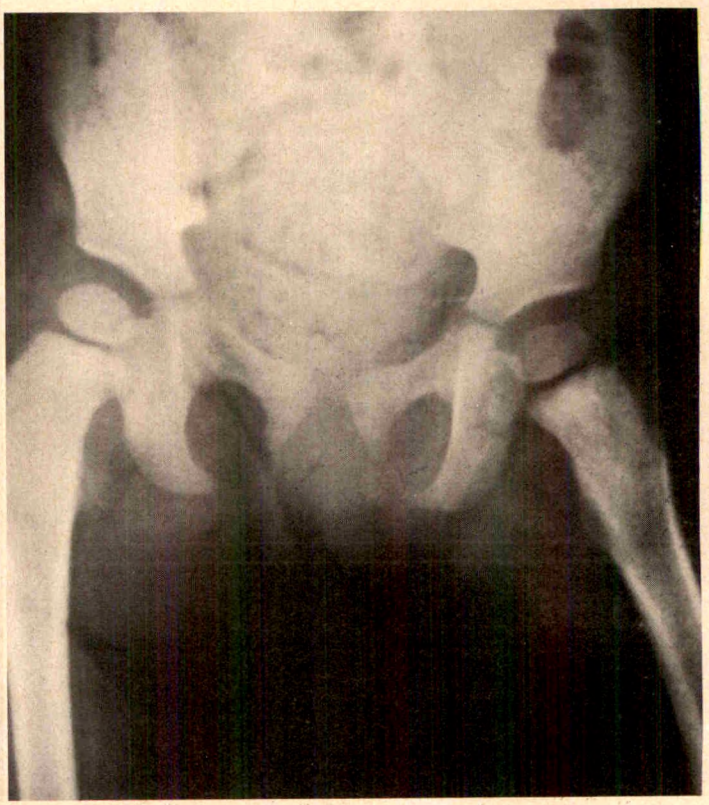


Fig 2.—Case 2. Left, Normal bone scintigram. Right, Roentgenogram on 21st hospital day, showing lytic lesions of proximal left femur. (Periosteal elevation along margin of left femur was visible on actual roentgenogram but is difficult to see on this reproduction.)



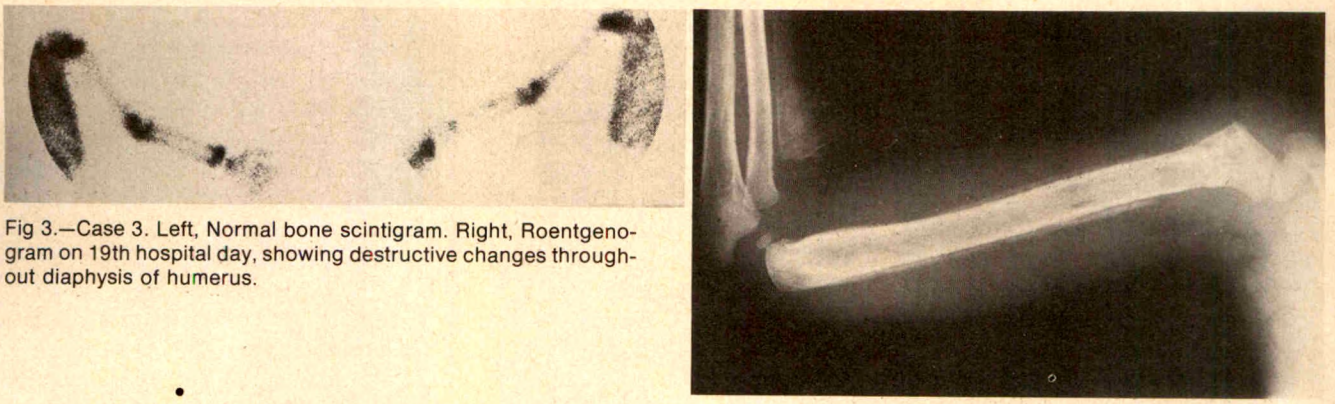


Fig 3.—Case 3. Left, Normal bone scintigram. Right, Roentgenogram on 19th hospital day, showing destructive changes throughout diaphysis of humerus.

On the 17th hospital day, a roentgenogram (Fig 1, right) showed a lytic lesion in the ilium adjacent to the left sacroiliac joint. At surgical exploration, there was a necrotic area in the ilium, pus in the sacroiliac joint, and an abscess cavity contiguous to this joint. The infected area was debrided and drained. Results of pathologic examination were consistent with acute osteomyelitis. Aerobic and anaerobic cultures of the pus and necrotic bone were sterile. The child received six weeks of nafcillin therapy and was discharged in good health. Repeated roentgenograms showed sclerosis at the site of the lytic lesion in the ilium.

Case 2.—A 22-month-old female infant was admitted to the Children's Hospital of Philadelphia, with a limp of two days' duration. She appeared mildly ill, and her temperature was 38.3 °C. She maintained her left lower extremity rigidly extended and resisted movement. Passive range of motion was full, but it elicited considerable pain. There was no point tenderness, swelling, erythema, or warmth of the spine, pelvis, hips, or femurs. The remainder of the physical examination showed no abnormalities.

The values for the laboratory studies were as follows: hemoglobin, 11.7 g/dL; hematocrit, 30%; and WBCs 12,000/cu mm, with 2% band forms, 70% neutrophils, 12% lymphocytes, 12% monocytes, and 1% eosinophils. The ESR (Wintrobe) was 46 mm at one hour, and electrophoresis showed hemoglobin AA_2. Roentgenograms of the chest, lumbosacral spine, sacroiliac joint, left hip, and left lower extremity were normal.

The child remained febrile on the second hospital day. A radionuclide scan using technetium Tc 99m pyrophosphate (Fig 2, left) was normal. Aspiration of the left hip joint under fluoroscopy yielded 0.5 mL of clear fluid that was Gram- and culture-negative. On the third hospital day, oxacillin sodium therapy was begun when the blood cultures taken on admission to the hospital had growths of *S aureus*. A gallium scan was normal. Ambulation returned gradually from the seventh to 14th hospital day. A roentgenogram (Fig 2, right) of the left femur on the 21st hospital day showed destructive bone changes in the left proximal femur and periosteal elevation along the shaft, both of which were consistent with osteomyelitis. She recovered uneventfully after six weeks of oxacillin therapy.

Case 3.—A 3-year-old boy with sickle cell anemia was admitted to the Children's Hospital of Philadelphia with right arm pain and fever of three day's duration. He appeared to be in considerable pain, and his temperature was 39 °C. His right forearm and wrist were swollen and tender. The results of the rest of the physical examination were normal.

Laboratory studies gave the following results: hemoglobin, 8.0 g/dL; hematocrit, 25%; and WBC count, 24,000/cu mm, with 9% band forms, 75% neutrophils, 8% lymphocytes, and 8% atypical lymphocytes. The ESR (Wintrobe) was 48 mm at one hour. A roentgenogram showed diffuse, soft-tissue swelling of the right arm.

The child was treated initially with ampicillin sodium. On the second hospital day, chloramphenicol sodium succinate and gentamicin sulfate were added to the patient's therapy when a Gram-negative rod was detected in the initial blood cultures. The organism was later identified as *Salmonella* C_1, which was sensitive to ampicillin, and the chloramphenicol and gentamicin treatments were discontinued. A technetium bone scan (Fig 3, left) was normal.

A needle aspiration of the patient's distal right humerus was performed on the fifth day. This yielded no pus, and cultures were sterile. On the 19th hospital day, a roentgenogram (Fig 3, right) of the child's right arm showed destructive changes throughout the diaphysis of the humerus, most likely the result of extension of infection originating at the metaphysis.

On the 35th day of ampicillin therapy, a second needle aspirate of the patient's humerus yielded bloody fluid containing many neutrophils. *Salmonella* C_1, sensitive to ampicillin, grew from a culture of this fluid, and chloramphenicol was added to the patient's therapy. Surgical drainage of the patient's distal humerus on the 43rd hospital day produced 10 mL of sterile pus from the subperiosteal and intramedullary spaces, which was sterile on culture.

After 57 days of ampicillin and 23 concurrent days of chloramphenicol therapy, the patient was discharged home with good mobility and no tenderness of his right arm. His ESR was 4 mm at one hour, and roentgenograms disclosed healing osteomyelitis and callus formation around a pathologic fracture.

COMMENT

Radionuclide scanning is generally recognized as a useful technique in the early diagnosis of osteomyelitis.[3-8] Although ordinary roentgenograms may not detect a destructive bone medullary lesion until it has reached a size of 1 to 1.5 cm and has resulted in a loss of 30% to 50% of bone matrix, scintigraphy often demonstrates variations in bone metabolism that may precede even the soft-tissue roentgenographic abnormalities.

In 1966, DeNardo[8] studied 18 patients with suspected osteomyelitis. The strontium scintigram was abnormal in all of the 13 confirmed cases, although five of them had normal roentgenograms. No patient had a falsely normal scintigram.

Recent experience with children has confirmed the reliability of radionuclide scanning. Letts et al[7] studied 20 children with suspected osteomyelitis who had normal roentgenograms. Of the 15 children with focally increased uptake of radionuclide by bone, 14 proved to have osteomyelitis, and one had a leukemic bone deposit. None of

the five children with normal bone scans had osteomyelitis. Treves et al[4] described eight children with infections of long bones, and Trauner and Connor[5] described two children with sacroiliac osteomyelitis, all of whom had diagnostic bone scans. Seventy of 71 children described by Gilday et al,[6] and all of the 34 patients reported by Majd[3] had radionuclide scans confirming the diagnosis of osteomyelitis.

Our three patients had proved osteomyelitis in spite of normal bone scans. A definite diagnosis was delayed in the first child with sacroiliac osteomyelitis because he was initially thought to have either an intra-abdominal abscess or a septic arthritis of the hip[9,10] and because two scintigrams, performed after four and seven days of symptoms, failed to demonstrate any abnormality. The recovery of *S aureus* from the blood, the appearance of bony destruction on roentgenograms, and the histologic findings of the bone biopsy specimen eventually confirmed the diagnosis.

In the second child, osteomyelitis was suspected initially because of the hip pain and limitation of motion in spite of normal results of a joint fluid examination. The positive blood cultures for *S aureus* and the later roentgenographic changes confirmed the clinical impression. Since bone aspiration yielded no pus, open surgical drainage and biopsy were not performed.

The isolation of *Salmonella* from the blood of the third child, who had sickle cell anemia and a painful swollen arm, strongly suggested osteomyelitis early in the hospitalization; however, a scintigram on the fifth day of symptoms was normal.[11] The positive culture from bone, the later roentgenographic abnormalities, and characteristic histologic findings verified the clinical diagnosis.

Review of the literature indicates that radionuclide scanning is a reliable method for the detection of osteomyelitis. Only one falsely normal scan occurred among 129 children with osteomyelitis reported by several authors.[3,6,7] An explanation for the occasional normal bone scan early in the course of osteomyelitis has been postulated.[12-14] It is suggested that inflammation spreading from within the marrow space may interfere with the blood supply to the metaphysis. Subsequent scintigrams may be abnormal, with involvement of the cortex and periosteum.

The exact role of scintigraphy in the diagnosis of osteomyelitis needs further definition. Our cases demonstrate that, on occasion, the bone scan does not show increased uptake in confirmed infections. The possibility of falsely normal scintigraphy emphasizes the importance of instituting antibiotic therapy, after cultures are taken, on the basis of a strong clinical suspicion of osteomyelitis.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*
Gentamicin sulfate—*Garamycin.*

References

1. Dich VQ, Nelson JD, Haltalin KC: Osteomyelitis in infants and children: A review of 163 cases. *Am J Dis Child* 129:1273-1278, 1975.
2. Capitanio MA, Kirkpatrick JA: Early roentgen observations in acute osteomyelitis. *Am J Roentgenol Rad Ther Nucl Med* 108:488-496, 1970.
3. Majd M: Radionuclide imaging in early detection of childhood osteomyelitis and its differentiation from cellulitis and bone infarction. *Ann Radiol* 20:9-18, 1977.
4. Treves S, Khettry J, Broker FH, et al: Osteomyelitis: Early scintigraphic detection in children. *Pediatrics* 57:173-186, 1976.
5. Trauner DA, Connor JA: Radioactive scanning in diagnosis of acute sacroiliac osteomyelitis. *Pediatrics* 87:751-753, 1975.
6. Gilday DL, Paul DJ, Patterson J: Diagnosis of osteomyelitis in children by combined blood pool and bone imaging. *Nuclear Med* 117:331-335, 1975.
7. Letts RM, Afifi A, Sutherland JB: Technetium bone scanning as an aid in the diagnosis of atypical acute osteomyelitis in children. *Surg Gynecol Obstet* 140:899-902, 1975.
8. DeNardo GL: The ^{85}Sr scintiscan in bone disease. *Ann Intern Med* 65:44-53, 1966.
9. Morgan A, Yates AK: The diagnosis of acute osteomyelitis of the pelvis. *Postgrad Med J* 42:74-78, 1966.
10. Young F: Acute osteomyelitis of the ilium. *Surg Gynecol Obstet* 58:986-994, 1936.
11. Ortez-Neu C, Marr JS, Cherubin S, et al: Bone and joint infections due to *Salmonella*. *J Infect Dis* 138:820-828, 1978.
12. Handmaker H, Leonards R: The bone scan in inflammatory osseous disease. *Semin Nucl Med* 6:95-105, 1976.
13. Russin LD, Staab EV: Unusual bone scan findings in acute osteomyelitis. *J Nucl Med* 17:617-619, 1976.
14. Testes CD, Williamson BRJ: Hot and cold bone lesion in acute osteomyelitis. *Am J Roentgenol* 129:517-518, 1977.

CORRECTION

Figure Printed by Mistake.—In the "Clinical Memorandum" titled "Symptomatic Hyponatremia in Nephrotic Syndrome," published in the February JOURNAL (134:204-206, 1980) a figure was incorrectly printed along with the article.

Trauma and Child Abuse

The Importance of the Medical Record

Gerald Solomons, MD

• **A chart audit was undertaken to ascertain the content and quality of documented information present in medical records of patients with traumatic injuries seen in a tertiary care hospital. Of the records of children younger than 6 years of age with a diagnosis of fracture, burn, contusion, or intracranial injury seen in the inpatient or outpatient services during a one-year period, 60% contained inadequate data on which to determine retrospectively if the medical diagnosis of child abuse was ever considered. The medicolegal implications of this are discussed.**

(*Am J Dis Child* 134:503-505, 1980)

Because of the increased incidence of reporting of child abuse and neglect, the health professional is appearing more frequently in court. The conduct and testimony of the medical witness in court have been the subject of several articles and audiovisual materials,[1-4] but the medical record has not been examined critically for content and quality. Many physicians, particularly interns and residents, have been appalled at the lack of information present in their patients' records after these documents, and they, have been subpoenaed. Juvenile court judges and attorneys have also complained of the lack of documentary evidence corroborating the verbal testimony of many of the professional witnesses. Cases have been dismissed because of lack of such evidence.

Of all the reported cases of child abuse in Iowa, a mere 3% are reported by physicians.[5] Because of this failure of health professionals to report, many state laws now include penalties such as fines and/or imprisonment; but despite these and the increase of information in professional journals and the lay press, there has not been a substantial increase in physician reporting.

Since 1976, 35 states have decreed criminal or civil penalties for failure to report child abuse.[6] In some states, the health professional may be liable for "the damages proximately caused" from failure to report, and the hospital record may be the evidence on which litigation is based.

The California Supreme Court decision in the Landeros case[5] allows litigation for malpractice if a full investigation for child abuse is not carried out for a patient with a diagnosis of suspected abuse. According to Zimmerly,[7] there are now two cases on record where parents accused of murder or negligence in the death of a child have brought malpractice action against the physician involved, claiming that lack of medical care rather than physical abuse caused death. Both actions failed, but there may be similar attempts in the future.

Many physicians are insensitive to the need to report the possibility of physical abuse in cases of trauma. There are several reasons. The commonest is ignorance of the law, its purpose, procedures, and penalties. Some physicians are just antagonistic towards it, viewing the law as an infringement on the rights of the individual. Many are erroneously frightened of being sued despite their immunity from civil and criminal liability. Excessive time in court; inadequate community programs for reported families, and disruption of the doctor-patient relationship are other explanations given for the physician's reluctance to "become involved." Irrespective of the reason, physicians cannot ignore their legal obligations of performing a comprehensive evaluation, reporting the case if they are suspicious of abuse, and supporting their decision by adequate documentation. This chart audit was undertaken to ascertain the content and quality of documented information present in

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medical records of patients with traumatic injuries seen in a tertiary care hospital.

METHODS

Records of all patients younger than 6 years of age with a diagnosis of fracture, burn, contusion, or intracranial injury seen in the inpatient or outpatient services of University of Iowa Hospitals and Clinics, Iowa City, between July 1, 1975, and June 30, 1976, were reviewed. To determine retrospectively if the diagnosis of child abuse had been considered in trauma cases, the medical records were reviewed for the presence of four criteria. These criteria are considered to be mandatory and the minimal amount of information necessary. The four mandatory items were: (1) history of the injury; (2) description of the injury; (3) documentation of previous injuries or accidents; and (4) compatibility or incompatibility between the history given and the injuries sustained. The latter was based on an assessment of all the information in the record and was either obvious, stated, or implied.

If any of the just-mentioned four criteria were absent, the record was considered to be inadequate. The records were also evaluated subjectively for the quality of the information contained in the four criteria.

RESULTS

There were 161 cases of fractures, burns, contusions, and intracranial injuries that were seen at University of Iowa Hospitals and Clinics in children younger than 6 years of age during a one-year period. Five records could not be located, leaving 156 charts available. Of these visits, 25 were for elective repair or follow-up of a previous condition. Five cases reported as child abuse were not included. The 126 remaining case records were reviewed (Table 1).

Adequacy of Information

According to the aforementioned criteria, 35 of 62 (56%) cases of fractures, seven of 18 (39%) cases of burns, 23 of 27 (85%) cases of contusions, and 11 of 19 (58%) cases of intracranial injury were considered to have inadequate information on retrospective examination of the medical records to determine the presence or absence of child abuse. It was impossible to determine from these records if that diagnosis had even been considered.

Table 1.—Trauma Cases of Children Less Than 6 Years Old

Recorded Status	Fractures	Burns	Contusions	Intracranial	Total
Elective follow-up	7	13	. . .	5	**25**
Abused	4	. . .	. . .	1	**5**
Not located	. . .	. . .	. . .	. . .	[5]*
Reviewed	62	18	27	19	**126**
Total available	**73**	**31**	**27**	**25**	**156**

*Not counted in total of available charts.

Table 2.—Description of Injury by Category of Trauma

	Fractures	Burns	Contusions	Intracranial	Total, No. (%)
Basic	1	. . .	2	. . .	**3** (2)
General	51	16	21	18	**106** (84)
Detailed	10	2	4	1	**17** (13)
Total	**62**	**18**	**27**	**19**	**126**

The overall number of cases in the total sample of 126 with inadequate information was 76 (60%). It is worth noting that patients with contusions, the most common injury sustained in physical child abuse, had the highest percentage of inadequate records.

Subjective Evaluation of the Quality of the Information

History.—The history of the injury is obviously most important. It varied from a one-word description "fall" to the detailed "3 foot fall from dresser to carpeted floor while being diapered." Ideally, where there is a suspicion of abuse, the parents should be questioned separately and a conflict or change in the stories should be noted.

Description of the Injury.—The records varied from a basic statement of "multiple bruises," to a detailed description of number, size, location, and appearance of all lesions, including drawings. Only 13% were so precisely described (Table 2).

This is the one criterion over which the physician does have complete control. The written record often has more credibility than a photograph of poor quality. The description of the injury receives a great deal of emphasis in court because of its importance in determining the severity, extent, and method by which the injury was sustained.

Documentation of Previous Injuries or Accidents.—This item was often left out but its need is apparent. Even if this episode of trauma was not considered as possible abuse, a history of several previous injuries or noxious ingestions during a short period of time might support the decision to report this as a case of neglect. Neglect is a reportable condition in 47 states and the District of Columbia.[6]

Compatibility Between History and Injury.—This was often obvious or implied from the circumstances of the injury, eg, automobile accident, playground injury, etc. On occasion, there was a statement that history and injury were compatible if child abuse was initially suspected and then excluded after evaluation. Only when the decision was made to report the case as child abuse was there a statement in the record that the history and injury were at variance or incompatible. In the majority of records, the descriptions of history and injury were so cryptic that no determination of compatibility or incompatibility could be determined.

COMMENT

From the aforementioned results, it would seem that the majority (60%) of records of traumatic injuries of children younger than 6 years who were seen in this hospital contain inadequate data on which to determine retrospectively if the medical diagnosis of child abuse was ever considered. Unfortunately, the court's decision is most often based on the information contained in that record. It is possible that the appropriate questions were asked and satisfactory answers were given, but they were not recorded; and

such omission can be critical when litigation occurs or disposition of a case is decided.

Too often, the history of the injury was cryptic: "Fall from second story window." "Fall down stairs." "Fell from car." "Pulled coffeepot on him." Little attempt was made to determine the height of the fall, the presence of a carpet on the floor to cushion the impact, or the reason for an infant to be at an open window. Despite medicolegal emphasis on careful description of all traumatic lesions, only 13% were precisely described.

If the history and the injury are not definitively described, the compatibility between history and injury is also in doubt. Incompatibility is probably the most important criterion on which to base a medical decision to report suspected abuse. Ambiguity in this crucial factor can be hazardous to the patient who is still in jeopardy, as well as to the physician who may be guilty of malpractice or failure to report because of lack of clarity or imprecision in the record. On July 1, 1978, the Iowa law regarding abuse of children was amended to give this definition of physical abuse: "any nonaccidental physical injury, or *injury which is at variance with the history given of it,* suffered by a child as the result of the acts or omissions of a person responsible for the care of the child." This in itself is sufficient reason for a written statement regarding compatibility.

Records were inadequate to determine if child abuse was considered in the diagnosis in 60% of the cases. This is far too high a figure, particularly in a university teaching hospital with an active educational program and a committee for child abuse and neglect.

There is a need for a simple protocol for all cases of trauma that specifically details the following: the manner in which the injury occurred; a description of the injuries, with diagrams; a statement regarding compatibility of history and injury; and a list of previous injuries.

The focus of this article is on child abuse. However, even if this diagnosis is excluded, many cases of trauma may still have possible legal consequences for the patient (damages), and the physician (malpractice). The content of the medical record would be equally important.

In the present climate of litigation and public awareness of child abuse, the physician must realize the necessity for accurate recording. It is readily acceptable that documentation of known cases of suspected abuse need to be precise, but it could be argued that evaluation and documentation on unsuspected cases need not be so meticulous. The Landeros case is a classical example of such faulty logic. The lack of suspicion of the physician at the time of examination may be due to an inadequate history or an inadequate workup. There is now enough written in the professional literature to set the standard for medical competence in this area, and all physicians will have to meet that standard. Therefore, the need for precise documentation in all cases of childhood trauma is now necessary because of the health professionals' vulnerability in this regard.

References

1. Leake HC, Smith DJ: Preparing for and testifying in a child abuse hearing. *Clin Pediatr* 16:1057-1063, 1977.
2. *We Can Help: A Curriculum on the Identification, Reporting, Referral and Case Management of Child Abuse and Neglect.* Unit 14: Specialized training for medical and health professionals, module 7: The medical witness in court. US Dept of Health, Education, and Welfare, National Center on Child Abuse and Neglect, 1976.
3. *The Battered Child Syndrome,* slide kit produced from the materials of Robert ten Bensel. New York, Medcom, 1971.
4. Levine M: You can overcome the frustrations in a battered-child case. *Med Econ* 3:129-138, 1976.
5. Solomons G, Young HA: Malpractice and child abuse. *J Iowa Med Soc* 68:239-243, 1978.
6. *Trends in Child Abuse and Neglect Reporting Statutes,* report No. 95. Child Abuse Project, Education Commission of the States. Denver, Education Commission of the States, 1977, pp 6-15.
7. Zimmerly JG: Physicians could get blame for child abuse. *Leg Aspects Med Pract* 6:3-4, 1978.

Familial Pulmonary Atresia

Its Occurrence With a Ventricular Septal Defect

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• To our knowledge, this is the first reported case of pulmonary atresia with a ventricular septal defect that occurred in a father and his son. A multifactorial mode of determination that resulted from an interaction between genetic predisposition and environmental factors was assumed, since the family history did not show other members with congenital heart defects. Based on the background and on information from the multifactorial theory of inheritance, a counseling plan was formulated for these parents. A similar approach is recommended for the many surgical survivors of previously uncorrectable complex congenital heart defects as they approach reproductive age.

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Successful surgical correction of complex cyanotic congenital heart defects has created a patient population that is reaching child-bearing age.[1] Concern has been raised about the risk of cardiovascular malformations in the progeny of these patients. The opportunity to document recurrence of a defect in the first generation offspring has been particularly difficult in the face of previously uncorrectable and lethal lesions.

We studied a father and his son, both with pulmonary atresia and a ventricular septal defect. After review of the literature, we concluded this to be the first time the defect had been reported in a father and son, neither of whom had surgical correction. It supports the theory that recurrences of complex lesions are possible and that genetic counseling will be essential for the surgical survivors of previously fatal cardiac defects.

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REPORT OF CASES

CASE 1.—A 2,400-g boy, born spontaneously at home to a 24-year-old gravida 3 para 2 mother, was admitted to a community hospital, where he was treated for pneumonia. He was subsequently transferred to the Intensive Care Unit of the Children's Hospital of Buffalo because of respiratory distress and progressive cyanosis. Evaluation showed the child to have pneumonia, atelectasis, and a pneumothorax. Despite respiratory improvement over the next five days, the child continued to be severely hypoxic. Because of continued cyanosis and the onset of a murmur, cardiac consultation was obtained.

The cardiovascular evaluation disclosed a pale, cyanotic infant with a right thoracotomy tube, a pulse rate of 150 beats per minute, and a blood pressure in both arms of 70/20 mm Hg. The precordium was relatively quiet to palpation. The first heart sound was normal, and the second heart sound was single. A grade 3/6 pansystolic murmur was detected at the second-left interspace, and there was no diastolic murmur. An apical gallop was easily audible. The liver was palpated 3 cm below the right costal margin. All peripheral pulses were bounding.

The ECG showed combined ventricular hypertrophy. Chest roentgenogram showed a large heart shifted to the left. There was atelectasis of the right-lower lobe and an infiltrate in the right-upper lobe. Although no pneumothorax was present, interstitial emphysema was observed. With the child breathing 80% oxygen, the arterial Po_2 was 25 mm Hg, the Pco_2 was 29 mm Hg, and the pH was 7.5. The echocardiogram showed a large aorta overriding the ventricular septum.

Cardiac catheterization revealed bidirectional ventricular shunting, with equal ventricular pressures. No obstruction was recorded across the aortic valve. Calculation of the pulmonary resistance was not possible because the pulmonary arterial vessels were not entered.

The cineangiograms demonstrated a large aortic root that was displaced far to the left. The aorta arose posteriorly from the left ventricle, arose to the midline, and descended on the right. The pulmonary circuit filled bilaterally via large, persistent, segmental pulmonary arteries that arose from the descending aorta (Fig 1). There were multiple pulmonary branch ste-

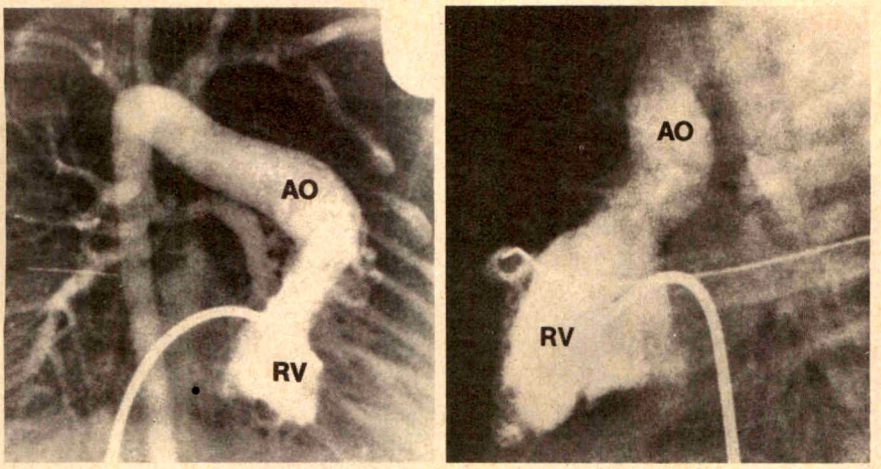

Fig 1.—Right ventriculogram (left, anteroposterior: right, lateral) in infant son showing trabeculated right ventricular (RV) cavity with contrast material streaming across ventricular defect into posteriorly located aorta. Long ascending aorta (AO) was displaced to left and descended on right. Primitive segmental pulmonary arteries arose from descending aorta. Right thoracotomy tube was positioned to relieve preexisting pneumothorax.

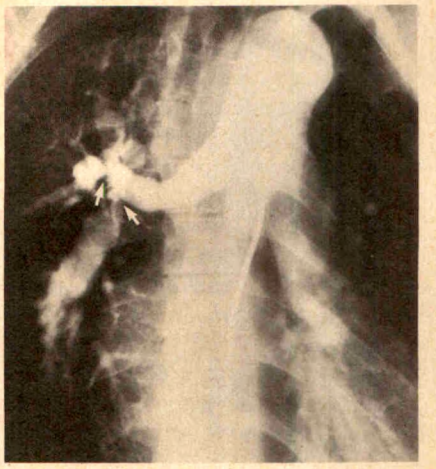

Fig 2.—Descending aortogram in 30-year-old father demonstrating large pulmonary vessels, with multiple-branch stenoses (arrows) on right.

noses. A patent ductus arteriosus was not noted.

The ventriculograms outlined a large interventricular septal defect. The left ventricle was large and posterior; the right ventricle was anterior, to the right, and heavily trabecular. There was absolutely no evidence of a right ventricular outflow tract.

The child was treated medically for his residual pulmonary problems and congestive heart failure. He did well and was discharged from the hospital. At the time of this writing, he was 26 months of age, growing slowly, but otherwise in a satisfactory condition.

CASE 2.—Review of the entire family history, including that of the sibling brother and sister, uncovered no other congenital heart defect except for that of the father. He was a 30-year-old man thought to have a truncus arteriosus type 4, documented by cardiac catheterization in 1961 at the Children's Hospital of Buffalo. He was first noted to have a murmur at the age of 5 months, was mildly cyanotic during childhood, and required neither medications nor surgical intervention. Presently, he reported very few physical restrictions except for fatigue on moderate to heavy exercise. He has been relatively asymptomatic, except for palpitations that began one year ago. In view of his clinical status and due to the recent advances in cardiac surgery, reevaluation and cardiac catheterization were recommended.

The physical examination showed a thin, 30-year-old adult male in no acute distress, but with moderate peripheral cyanosis and clubbing. A blood pressure of 130/40 mm Hg was recorded in both arms. The pulse rate was 96 beats per minute and regular. All pulses were bounding. The point of maximum impulse was palpable in the sixth interspace at the anterior axillary line. There was a prominent apical ventricular lift. No thrills were palpated. A grade 3/6 harsh ejection systolic murmur could be heard over the left sternal edge radiating to the apex. An early diastolic blowing grade 2/6 murmur was auscultated over the same distribution. Continuous murmurs were heard over both lung fields, especially on the right. A loud ejection click was audible at the apex.

Chest roentgenogram showed a large cardiac silhouette with a very prominent aorta descending on the left. The pulmonary artery could not be identified. The pulmonary vascular markings were normal. An arterial blood sample, with the patient breathing room air, demonstrated a Po_2 of 50 mm Hg, a Pco_2 of 39 mm Hg, and a pH of 7.4. The echocardiogram showed a large aorta overriding the ventricular septum. Loss of the septal echoes just below the aortic root suggested a ventricular septal defect. The presence of a normal left atrium in a patient with a truncus arteriosus indicated normal to restricted pulmonary blood flow.

Cardiac catheterization showed that both ventricles were at equal pressures and demonstrated bidirectional shunting. The systemic arterial saturation was 85%. There was no truncal valve obstruction. A 15-mm Hg peak systolic pressure gradient was recorded on pullback from the pulmonary arteries to the descending aorta. The pulmonary resistance of 14.1 units/sq m was 45% of the systemic resistance.

The left ventriculogram outlined a large ventricular septal defect and aortic-mitral continuity. A very large aortic root overrode the ventricular septum. There was no evidence of a patent ductus arteriosus, but very large segmental pulmonary arteries with branch stenoses arose bilaterally from a left descending aorta (Fig 2). No trace of a right ventricular outflow tract or main pulmonary artery could be identified. These findings reclassified the father as having a pulmonary atresia with a ventricular septal defect. Because of the high risk category of this patient and his reluctance to pursue surgery, no further intervention was recommended.

COMMENT

To our knowledge, this report is the first instance of pulmonary atresia with a ventricular septal defect that occurred in a parent and child. Since only a small percent of all patients with this anomaly survive without surgical intervention, little is known of the recurrence risks. The unusually well-balanced hemodynamic state in the case of the father has provided the rare opportunity to document a recurrence in this family.

Similar morphologic patterns have stirred much controversy in the literature over the terminology and classification of this combination of defects. Several classifications have been proposed, including the following: pulmonary atresia with a ventricular septal defect, Fallot's tetralogy with severe right-ventricular outflow hypoplasia, truncus arteriosus type 4, and pseudo-

truncus.[2-6] We have elected to classify these two patients as having pulmonary atresia with a ventricular septal defect, predominantly on the basis of the arterial blood supply to the lungs.[7,8] Both patients had large persistent segmental or primitive pulmonary arteries. They arose from the descending aorta and bifurcated in a pattern identical to pulmonary arteries. Large segmental arteries of this type have been reported in as many as 25% of all patients with pulmonary atresia.[9,10] In addition, a main pulmonary artery could not be demonstrated angiographically. Total absence of the right ventricular outflow tract further qualified both hearts as having pulmonary atresia with a ventricular septal defect rather than Fallot's tetralogy.

Congenital heart defects occur in about eight per 1,000 births each year.[11] Approximately 1% of these are due to single mutant gene, as exemplified by the Holt-Oram syndrome; 4% have gross chromosomal abnormalities, as seen in patients with trisomy; and the remaining 95% are attributed to multifactorial inheritance.[12-14] The multifactorial hypothesis implies interaction between multiple genetic and environmental factors. A complete review of both maternal and paternal families showed no other history of congenital heart defects. All possible etiological factors, including advanced reproductive age in grandparents, maternal exposure to radiation, infection, drugs, high altitude, and other known environmental teratogens, were excluded.

In view of this information, two important questions involving the genetic counseling of this family may be answered. The first is the risk of the parents having further children with congenital heart defects, and the second is the empirical risk of the proband son doing the same. The multifactorial mode of inheritance would suggest at least a 10% risk of recurrence of a congenital heart defect in another child. This risk factor increases with the number of affected first-degree relatives.[15] To illustrate this relationship, if only the father were affected, there would be a 3% to 5% chance of recurrence in his offspring. With the addition of a second case in his son, the risk increased to at least 10%. On the other hand, the recurrence risk to the offspring of the affected son still is of the order of 3% to 5%. Although multifactorial determination is the most likely explanation, the possibility of a rare gene mutation manifested as an autosomal dominant trait cannot be excluded. This would imply a 50% risk of recurrence for any child of an affected person. This possibility emphasized a need for caution in counseling for rare traits.

The survival of this father to reproductive age has provided documentation of a recurring congenital heart defect in his son. Although this is indeed a rare event, the emergence of surgical survivors of previously lethal cardiac defects into child-bearing age makes the question of inheritance even more crucial. These patients will allow a more explicit view into the true incidence, as well as the causes of, these previously fatal and uncorrectable conditions. The clinician must be increasingly aware of the recurrence risks and should focus as deeply on the familial evaluation as he does on the medical and surgical aspects of the defect.

References

1. Nora JJ, Dodd PF, McNamara DG, et al: Risk to offspring of parents with congenital heart defects. *JAMA* 209:2052-2053, 1969.
2. Stukey JD, Bowdler JD, Reye RD: Absent sixth aortic arch: A form of pulmonary atresia. *Br Heart J* 30:258-264, 1968.
3. Collett RW, Edwards JE: Persistent truncus arteriosus: A classification according to anatomic types. *Surg Clin North Am* 29:1245-1270, 1949.
4. Crupi G, Macartney FJ, Anderson RH: Persistent truncus arteriosus: A study of 66 autopsy cases with special reference to definition and morphogenesis. *Am J Cardiol* 40:569-578, 1977.
5. Van Praagh R, Van Praagh S: The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryological implications. *Am J Cardiol* 16:406-425, 1965.
6. Van Praagh R: Classification of truncus arteriosus communis (TAC). *Am Heart J* 92:129-132, 1976.
7. McGoon MD, Fulton RE, Davis GD, et al: Systemic collateral and pulmonary artery stenosis in patients with congenital pulmonary valve atresia and ventricular septal defect. *Circulation* 56:473-479, 1977.
8. Macartney FJ, Scott O, Deverall PB: Hemodynamics and anatomical characteristics of pulmonary blood supply in pulmonary atresia with ventricular septal defect, including a case of persistent fifth aortic arch. *Br Heart J* 36:1049-1060, 1974.
9. Somerville J: Management of pulmonary atresia. *Br Heart J* 32:641-651, 1970.
10. Jefferson K, Rees S, Somerville J: Systemic arterial supply to the lungs in pulmonary atresia and its relation to pulmonary artery development. *Br Heart J* 34:418-427, 1972.
11. Mitchell SC, Korones SB, Berendes HW: Congenital heart disease in 56,109 births. *Circulation* 43:323-332, 1971.
12. Nora JJ, Meyer TC: Familial nature of congenital heart disease. *Pediatrics* 37:329-334, 1966.
13. Nora JJ: Multifactorial inheritance hypothesis for the etiology of congenital heart disease: The genetic-environmental interaction. *Circulation* 38:604-617, 1968.
14. Nora JJ, Spangler RD: Risks and counseling in cardiovascular malformations, in Bergsma D (ed): *The Fourth Conference on the Clinical Delineation of Birth Defects*. Baltimore, Williams & Wilkins Co, 1972, pp 154-159.
15. Nora JJ, Wolf RR: Recurrence risks in the family, in Kidd BSL, Rowe RD (eds): *The Child with Congenital Heart Disease After Surgery*. Mount Kisco, NY, Futura Publishing Co Inc, 1976, pp 455-457.

Phosphate Poisoning Complicating Treatment for Iron Ingestion

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• A 15-month-old child was treated for iron intoxication with a hypertonic sodium phosphate mixture. Clinical deterioration manifested by fever, obtundation, abdominal distention, dehydration, and hypotension followed soon after the administration of this mixture. Such symptoms may occur with either iron overdosage or with phosphate poisoning. At this time, the patient's serum chemistry values included: iron, 49 μg/dL; phosphorus, 24.6 mg/dL; and calcium, 4.5 mg/dL. The hypocalcemia, hyperphosphatemia, and dehydration were treated with parenteral gluconate calcium, intravenous fluids, and general supportive measures. Although the child had an uneventful recovery despite severe phosphate poisoning, therapeutic alternatives, such as sodium bicarbonate, should be used as adjuncts in the treatment of acute iron ingestion.

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Hypertonic phosphate solutions are recommended in the management of iron ingestion to decrease iron absorption through the production of poorly soluble ferrous phosphate.[1] Despite widespread use, a safe dose for children has not been determined. Hypertonic phosphate therapy may be hazardous if excessive amounts are absorbed, with resultant hyperphosphatemia with hypocalcemia and hyperosmolarity. As signs of hypertonic phosphate toxic reaction such as obtundation, abdominal distention, dehydration, and hypotension are similar to those of iron poisoning, a complication related to this therapy for iron ingestion may go unnoticed, thereby increasing the morbidity of iron overdosage. The present report emphasizes the potential danger of phosphate therapy for a patient with mild iron intoxication.

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REPORT OF A CASE

A 15-month-old boy ingested an unknown amount of iron tablets three hours prior to admission. While at home, he vomited twice. Pill particles were noted in the vomitus. Emesis was induced on admission to the hospital, and the vomitus was noted to be free of pill fragments. Initial physical examination showed an alert, active 10-kg child. Temperature was 36.6 °C; pulse rate, 120 beats per minute; respiratory rate, 32/min; and blood pressure, 80/50 mm Hg. The child was well-hydrated, with a soft, nondistended abdomen and a clear sensorium. The patient was thus admitted for observation. At admission, laboratory studies included a serum iron level of 281 μg/dL (normal, 50 to 150 μg/dL) and a hematocrit reading of 38%.

The patient remained asymptomatic until 12 hours postingestion when he passed a bloody stool. Results of his physical examination were unchanged from those at admission. Therapy with intravenous fluids was begun, using 5% dextrose in water with 25 mM/L NaCl and 20 mM/L KCl at a rate of 150/mL/kg/day. In addition, 60 mL of a buffered mixture of sodium biphosphate and sodium phosphate (Fleet Phospho-Soda) were administered orally. The child immediately vomited 30 to 45 mL of clear fluid. In retrospect, it was learned that the solution had been given undiluted at a 66% concentration.

Three hours later, the patient became acutely obtunded, with labored respirations, severe abdominal distention, dehydration, hypotension, and a fever of up to 40.9 °C. On ECG, the QT interval corrected for heart rate (QT_c) was prolonged (0.50 s). Serum laboratory studies disclosed the following values: iron, 49 μg/dL; calcium, 4.5 mg/dL; phosphorus, 24.6 mg/dL; albumin, 4.5 g/dL; sodium, 150 mM/L; potassium, 3.2 mM/L; bicarbonate, 13 mM/L; BUN, 41 mg/dL; and creatinine, 0.8 mg/dL. The hematocrit reading was 35%. A 10% solution of gluconate calcium (1.7 g) was given intravenously during a period of five minutes, and parenteral fluids were changed to 10% dextrose in water with 75 mM/L NaCl and 30 mM/L KCl at a rate of 250 mL/kg/day. The patient showed dramatic clinical improvement within four hours and serum chemical values returned to normal within 18 hours. A total of 5.0 g of gluconate calcium was administered. Recovery was uneventful.

COMMENT

Toxic reactions to hypertonic phosphate solutions have been reported for patients with diminished renal func-

tion,[2-5] gastrointestinal (GI) anomalies,[6-9] and meningomyelocele.[10] Hyperphosphatemia, hypocalcemia, and hyperosmolarity were reported in a 2-year-old child given 1,380 mL of an 11% phosphate solution by gastric lavage for the management of iron poisoning.[11] In addition, normal adults have had hyperphosphatemia within three hours of receiving an oral phosphate mixture in preparation for roentgenographic studies.[12]

Clinical deterioration in the present case was associated with the administration of a highly concentrated phosphate solution. The oral preparation used contains 48 g of sodium biphosphate and 18 g of sodium phosphate per deciliter, a sodium concentration of 4.83 mM/L, and a phosphate concentration of 394 mg/mL (J. D. Stevenson, C. B. Fleet Company, Inc, written communication, Feb 8, 1979). We estimate that our patient retained between 6 and 12 g of the 24 g of phosphate given as well as appreciable amounts of sodium. In the other reported case of hyperphosphatemia complicating iron poisoning,[11] the patient received a total of 84 g of phosphate by continuous lavage; but the amount, if any, of solution retained in the stomach postlavage was not specified. Toxic reaction has been reported in a 5-kg infant who was given only 4.1 g of phosphate.[13] Current recommendations for the management of iron poisoning vary from no mention of phosphate solutions[14] to gastric lavage with a 5% phosphate solution until the return is clear, followed by instillation of 150 mL of the same solution.[15] This instillate alone provides 4.5 g of phosphate, with the potential for exposure to large amounts depending on the volume of lavage. Disregarding errors in dilution as occurred in the present case, current recommendations for phosphate therapy may result in an unwanted toxic reaction. If the use of phosphate solutions is to continue, a safe dose per unit weight must be determined.

Manifestations of hypertonic phosphate poisoning observed in the present case included fever, obtundation, abdominal distention, dehydration, and hypotension. Laboratory studies confirmed hyperphosphatemia, hypocalcemia, hyperosmolar dehydration, acidosis, and hypokalemia. These findings are similar to the toxic reactions described with moderate to severe iron ingestion, and until laboratory results were known, there was considerable confusion regarding the seemingly inexplicable clinical deterioration. The low serum iron level, the temporal relation between clinical deterioration and phosphate administration, and the rapid improvement with calcium and fluid therapy implicate the hypertonic phosphate solution rather than iron poisoning as the cause of these findings.

Symptoms related to hypertonic phosphate poisoning are probably secondary to the high phosphate load with subsequent hypocalcemia as well as to the hypertonicity of the solution. The mechanism by which hyperphosphatemia results in hypocalcemia is unclear, but it may be related to increased extravascular precipitation of calcium.[16] Hypertonic dehydration is secondary to GI water loss and possible absorption of excess sodium. Although hypocalcemia may complicate hypertonic dehydration,[17] serum levels as low as 4.5 mg/dL would not be expected. Renal clearance of phosphate may be impaired by dehydration, but serum levels as high as 24.6 mg/dL would be unlikely to accrue from dehydration alone. Hypokalemia can be seen with either hypertonic dehydration or hypertonic phosphate poisoning.[18]

That reports of complications associated with therapy with a hypertonic phosphate mixture used in the management of iron intoxication are scarce may reflect an unrealized toxic condition. Absorption of phosphate may be enhanced across an intestinal mucosal barrier that is disrupted by the direct irritant action of ingested iron. This factor combined with the lack of an established safe dosage of the phosphate mixture should direct medical personnel treating iron overdosage to use alternative methods of iron-binding, such as 1% sodium bicarbonate. Our case and that of Bachrach et al[11] demonstrate that phosphate should not be used in the management of acute iron ingestion.

References

1. Stein M, Blayney D, Feit T, et al: Acute iron poisoning in children: University of California, San Diego, and University Hospital, San Diego (specialty conference). *West J Med* 125:289-297, 1976.
2. Oxnard SO, O'Bell J, Grupe WE: Severe tetany in an azotemic child related to a sodium phosphate enema. *Pediatrics* 53:105-106, 1974.
3. Chesney RW, Haughton PB: Tetany following phosphate enemas in chronic renal disease. *Am J Dis Child* 127:584-586, 1974.
4. Zipser RP, Bischel MD, Abrams DE: Hypocalcemic tetany due to sodium phosphate ingestion in acute renal failure. *Nephron* 14:378-381, 1975.
5. Ayala G, Chertow BS, Shah JH, et al: Acute hyperphosphatemia and acute persistent renal insufficiency induced by oral phosphate therapy. *Ann Intern Med* 83:520-521, 1975.
6. Moseley PK, Segar WE: Fluid and serum electrolyte disturbances as a complication of enemas in Hirschsprung's disease. *Am J Dis Child* 115:714-718, 1968.
7. Levitt M, Gessert C, Finberg L: Inorganic phosphate (laxative) poisoning resulting in tetany in an infant. *J Pediatr* 82:479-481, 1973.
8. Honig PJ, Holtzapple PG: Hypocalcemic tetany following hypertonic phosphate enemas. *Clin Pediatr* 14:678-679, 1975.
9. Loughnan P, Mullins GC: Brain damage following a hypertonic phosphate enema. *Am J Dis Child* 131:1032, 1977.
10. Sotos JF, Culter EA, Finkel MA, et al: Hypocalcemic coma following two pediatric phosphate enemas. *Pediatrics* 60:305-307, 1977.
11. Bachrach L, Correa A, Levin R, et al: Iron poisoning: Complications of hypertonic phosphate lavage therapy. *J Pediatr* 94:147-149, 1979.
12. Wiberg JJ, Turner GG, Nuttall FQ: Effect of phosphate or magnesium cathartics on serum calcium: Observations on normocalcemic patients. *Arch Intern Med* 138:1114-1116, 1978.
13. Smith MS, Feldman KW, Furukawa CT: Coma in an infant due to hypertonic sodium phosphate medication. *J Pediatr* 82:481-482, 1973.
14. Anderson JA, Narasimhan MJ Jr: Chemical and drug poisoning, in Vaughan VC III, McKay RJ, Nelson WE (eds): *Nelson Textbook of Pediatrics*, ed 10. Philadelphia, WB Saunders Co, 1975, pp 1672-1673.
15. Dreisbach RH: *Handbook of Poisoning: Diagnosis and Treatment*, ed 9. Los Altos, Calif, Lange Medical Publications, 1977, p 426.
16. Hebert LA, Lemann J Jr, Petersen JR, et al: Studies of the mechanism by which phosphate infusions lower serum calcium concentration. *J Clin Invest* 45:1886-1894, 1966.
17. Finberg L: Hypernatremic (hypertonic) dehydration in infants. *J Engl J Med* 289:196-198, 1973.
18. Forman J, Baluarte J, Gruskin AB: Hypokalemia after hypertonic phosphate enemas. *J Pediatr* 94:149-152, 1979.

Radiological Case of the Month

Lionel W. Young, MD; Contributed by Dennis W. Ross, MD, PhD

A 7-year-old boy with a two-year history of acute lymphoblastic leukemia was hospitalized for evaluation of fever, malaise, cough, rash, and dyspnea. His leukemia was believed to be in remission while he was on maintenance therapy of prednisone and methotrexate.

The present illness started four days prior to admission with fever, malaise, and erythematous rash initially on the face but later extending to the neck and trunk. There was a questionable history of measles one year previously. On physical examination he was an acutely ill dyspneic child with tachycardia, tachypnea, a temperature of 39 °C, and an erythematous maculopapular rash. No Koplik spots were seen. Diffuse rales over both lungs were heard. A chest roentgenogram (Fig 1) was obtained. Arterial blood gas levels were Po_2, 58 mm Hg, Pco_2, 28 mm Hg, and pH, 7.45.

His condition did not improve over 24 hours while receiving antibiotics and O_2 therapy, and an open lung biopsy was performed primarily to exclude *Pneumocystis carinii* infection. A wedge of tissue from the left upper lobe was resected. Microscopic findings are shown in Fig 2 and 3.

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Figure 1.

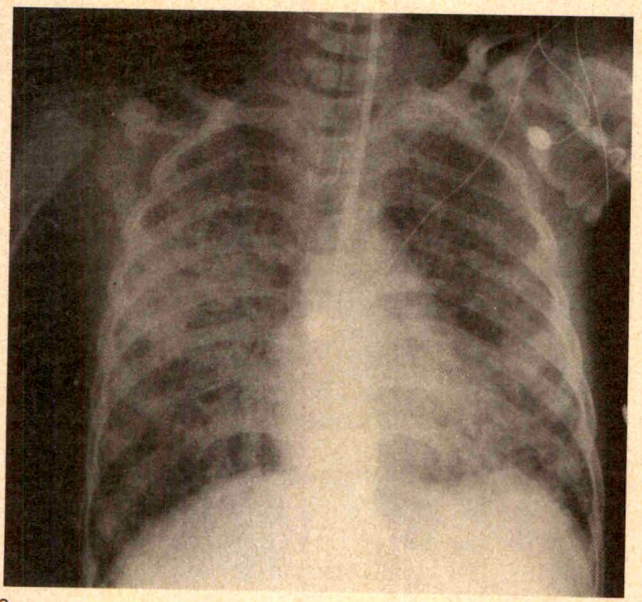


Figure 2.

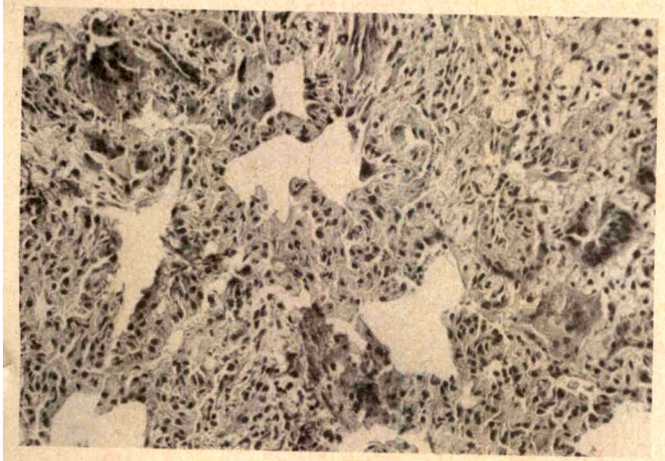
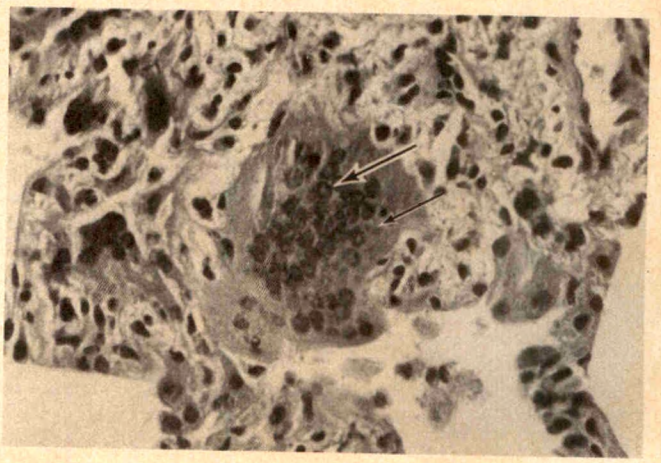


Figure 3.



Denouement and Discussion

Fig 1.—Posteroanterior roentgenogram showed diffuse interstitial and alveolar densities in lungs. Heart and mediastinum were normal.

Fig 2.—Biopsy specimen of lung showed diffuse interstitial infiltration characterized by numerous multinucleated giant cells lining alveolar air spaces.

Fig 3.—At high power, giant cells were seen to contain both nuclear (large arrow) and cytoplasmic (small arrow) inclusions.

Giant Cell Pneumonia

The diagnosis of giant cell pneumonia in this patient was made on the basis of the biopsy specimen. In children, pneumonia characterized by an interstitial infiltrate and the presence of multinuclear giant cells with intranuclear and intracytoplasmic inclusion bodies was first described as the entity "giant cell pneumonia" by Hecht.[1] Enders et al[2] and Mitus et al[3] showed this entity to be due to infection with rubeola virus in seven chronically ill patients, five of them with acute leukemia. Two unusual features consistently occurred in their patients: the persistence of viral particles lasting several weeks, and the failure to respond to the infection by the formation of measles complement fixing and neutralizing antibodies. Shah et al[4] recently reported four additional cases of giant cell pneumonia occurring in children with acute lymphoblastic leukemia in remission, three of whom died and one of whom survived. Roentgenographic signs usually preceded respiratory failure. Anderson and Kissane[5] characterize giant cell pneumonia with the constellation of findings: leukemic child, interstitial pneumonia with giant cells, persistence of virus, and no rise in antibody titer as an example of an unusual infection in the compromised host.

Our patient, as in the previously reported cases, showed the following: persistence of virus in the oropharynx as demonstrated by viral cultures; failure to demonstrate an antibody response to infection; and death from progressive anoxia (three weeks after the diagnosis). At autopsy the lungs showed diffuse, noticeable pulmonary fibrosis and no giant cells were observed. Bone marrow examination showed no morphologic evidence of active leukemia.

References

1. Hecht V: Die Riesenzellen pneumonia in Kindesalter, eine historische-experimentelle Studie. *Beitr Z Pathol Anat* 48:263-310, 1910.
2. Enders JF, McCarthy K, Mitus A, et al: Isolation of measles virus at autopsy in cases of giant cell pneumonia without rash. *N Engl J Med* 261:875-881, 1959.
3. Mitus A, Enders JF, Craig JM, et al: Persistence of measles virus and depression of antibody formation in patients with giant cell pneumonia after measles. *N Engl J Med* 261:882-889, 1959.
4. Shah KJ, Lewis MJ, Cameron AH, et al: Giant cell pneumonia complicating acute lymphoblastic leukemia in remission. *Ann Radiol* 20:79-86, 1977.
5. Anderson WAD, Kissane JM: *Pathology*, ed 7. St Louis, CV Mosby Co, 1977, pp 476-478.

The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Review

Vegetarianism in Children

William C. MacLean, Jr, MD, George G. Graham, MD

Vegetarians fall into four main subgroups. The distinction is of practical importance in that the more strictly vegetarianism is adhered to, the more difficult it becomes to assure an adequate diet for infants and children. Lactoovovegetarians exclude meat from the diet although some will eat fish. Milk and eggs are eaten with varying frequency but generally on a regular basis. Lactovegetarians refuse to eat eggs but will drink milk. Pure vegetarians reject any food of animal origin, including milk and eggs. One frequently sees pure vegetarians referred to as vegans. This term is probably better reserved for a subset of vegetarians whose philosophy precludes not only the consumption of foods of animal origin but also the use of any product of animal origin if a substitute exists. The proscription of animal products precludes the use of wool sweaters or leather shoes, for example. In addition to these obvious exclusions, things, such as honey and some cosmetics, whose relation to their animal origins is less obvious are also avoided.

Several points should be made about this classification. Individual vegetarians frequently do not fall conveniently into any one category. Some lactovegetarians or "pure" vegetarians may eat fish. Ovovegetarians who do not drink milk also exist. Second, many people who espouse vegetarianism do so gradually, first removing red meat from the diet, later fish, then milk and eggs. It is not surprising that there is an evolution toward more pure forms of vegetarianism in many cases. Any radical change in diet is difficult to accept and many people ease themselves progressively into more strict vegetarianism in much the same way that casual joggers slowly evolve into marathon runners. Interviews with vegans show a gradual change of philosophy during periods of five to ten years, moving from less strict to more strict vegetarianism and then by logical extension to veganism.[1] Since parents are the prime determinants of their children's diets it is important not simply to identify the vegetarian parent and child but to become aware of the evolution in dietary habits within the family. Since most forms of vegetarianism are compatible with normal growth and good health if certain precautions are taken, updating the history of dietary preferences is particularly important for anticipatory guidance. Finally, people attracted to vegetarianism may also be advocates of other forms of diet therapy, such as megavitamin therapy, natural foods, etc. Some of these practices are potentially harmful in normal children, especially younger infants, and may affect the approach parents will take to traditional medical therapy of illness.

Caring for vegetarian children generally means understandng and communicating with vegetarian parents. Hence, it is useful to look at the reasons people are drawn to vegetarianism. Some religious groups have traditionally been vegetarian. Several of the Indian religions include vegetarianism among the tenets of faith. Although immigrants from India to the United States are relatively small in number, in Great Britain there is a large number of vegetarians of Indian origin. In this country, Seventh-Day Adventists are perhaps the largest traditional religious group following vegetarianism. They are generally lactovegetarians or lactoovovegetarians. Although data are lacking, one might expect fewer nutritional problems from more stable groups in which the precepts of vegetarianism have been passed through successive generations.

The increasing concern for health and nutrition in the past decade has produced the so-called new vegetarians. The presumed health benefits range from decreased incidence of stroke and heart disease to changes in the prevalence of cancer of the colon. In a study of 100 new vegetarians, 35% cited health as a major reason for becoming vegetarians.[2] Day to day health, alertness, and mental functioning were as important as long-term disease prevention. Ethical (25%), metaphysical (14%), and ecological (8%) reasons were also cited. Attitudes on health-related questions were instructive: 55% considered cooking and/or eating a religious or philo-

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sophical experience, 31% followed specific dietary teachings, and 66% fasted occasionally but only 26% did so more than once a month. About a quarter of those surveyed took vitamin and mineral supplements regularly. A similar proportion used prescription medication. Finally, 20% mentioned the cost of food as a factor in their decision.

Dwyer and her co-workers,[2] who carried out the study, found substantial differences between those who had a close affiliation with a vegetarian group (termed "joiners") and those not so affiliated ("loners"). Joiners generally had dietary proscriptions that extended beyond vegetarianism per se to questions of organic or natural food and food processing. The patterns of food avoidance varied considerably from group to group. Also noteworthy was the tendency of joiners to attribute symptoms of illness to diet and to seek unorthodox medical care.

A survey of English vegans showed that only 9% approved of routine immunization, whereas 38% sanctioned blood transfusions. This compared with figures of 91% and 97%, respectively, among the population at large.[1] Such studies point up the complexities of dealing with vegetarian parents and the need to inquire about philosophical beliefs as they relate to diet and life-style.

POTENTIAL NUTRITION PROBLEMS

Adequacy of Dietary Protein

Protein quality refers primarily to the amino acid composition of a dietary protein, specifically how closely the concentrations of the essential amino acids come to meeting the requirements of the individual. In practice, dietary proteins are compared with a reference pattern[3] of an ideal protein. When viewed in this fashion, all vegetable proteins have a lower percentage of total nitrogen as essential amino acids and all are relatively deficient in one or more of the essential amino acids. Cereal grains, such as wheat, rice, and corn, all have a low lysine content relative to the other essential amino acids. Legumes, soy protein for example, are low in methionine. These amino acids are termed the first limiting amino acid for the proteins in question.

Complementarity occurs when the first-limiting amino acid of one protein is supplied in sufficient quantities by another protein to offset the deficit. The cereal-legume dietary combinations that have supported traditional societies for centuries are examples of complementarity: cereals tend to be good sources of methionine, legumes good sources of lysine. Eaten in combination the resulting protein quality is higher than that of either individual protein. Thus, although protein quality is of concern in vegetarian diets, especially in those of growing children, whose requirements are higher, this need not be a problem if cereals and legumes are eaten in combination. In some instances, the supplementation of a vegetable protein with its first-limiting amino acid, as is done with the addition of methionine to soy protein isolate-based infant formulas, corrects the essential amino acid deficiency. Similarly, supplementation of wheat with lysine results in dramatic increases in nitrogen retention.[4] In contrast, the addition of lysine to rice is not nearly so effective. This is so because threonine is nearly as limiting as lysine in rice protein, and because the low content of protein in rice and its poor protein digestibility are probably more important in limiting its nutritional value.

Quantity of dietary protein is also a potential problem. This relates as much to questions of digestibility as to the actual protein content of many common staple foods. Healthy infants thrive on human milk, in which approximately 6% of the total energy is derived from protein. When protein requirements are stated in terms of high-quality animal protein, 8% protein calories is generally believed to be a safe level of intake.[5] Legumes provide approximately 20% to 25% of the calories as protein; wheat, 10% to 15%; potato, 6% to 9%; and rice, 7% to 8%. In theory then, cereal-legume-based diets have the potential to provide more than adequate amounts of protein. In practice, the poor relative digestibility of many of the proteins in question, unless the food is highly processed, substantially reduces the amount of nitrogen actually absorbed from these sources.

Legumes have the highest protein content of the vegetables. Mean apparent nitrogen absorption in a group of children consuming a processed bean mixture, however, was only 66%, which is only three quarters that of the apparent absorption from a casein-based diet.[6] In contrast, the digestibility of the soy protein isolate used in infant formulas is excellent.[7]

Wheat provides an interesting example of the effects of processing on digestibility. Whole wheat has a higher protein content and quality than the white flour milled from it. The lower digestibility of whole wheat, however, effectively offsets the increase in protein intake from consuming whole wheat, making white flour an essentially equal source of net dietary protein.[8] Thus, whole wheat products, though endowed with "more nutrition," are often not well tolerated by younger children, whereas products based on milled wheat, such as pasta, are easily digested.[9] Rice protein is less well digested than processed wheat protein and this is not altered to any degree by processing. This is due to the fact that rice protein is present in the grain in small protein bodies that are resistant to digestion and that pass partially undigested in the stool.[10]

The discussion of protein adequacy pertains primarily to pure vegetarians. Rapidly growing infants and children have much higher amino acid requirements than adults. The sheer bulk of some sources of vegetable protein makes it difficult to maintain adequate intakes. Protein adequacy is hardly ever an issue in the lacto-ovovegetarian or lactovegetarian. Brown et al,[11] for example, found in their metabolic study of Bangladeshi children that the addition of as little as 25 mL/kg of milk to a traditional rice-vegetable diet increased protein intakes by 62% and increased apparent nitrogen retention by more than 400%. These results are explained by the fact that total nitrogen content rather than the concentration of any essential amino acid is first limiting in milk protein.[12] This relative excess of essential amino acids in milk results in a disproportionately large improvement in the use of vegetable protein. For this reason, the consumption of several glasses of milk with or without the occasional egg ensures adequate protein nutriture in all vegetarian children.

Adequacy of Energy Intake

Maintenance of adequate energy intake in vegetarian children is difficult for three reasons: the bulkiness (ie, low-energy density, kcal/g) of most staple foods, the poor energy digestibility of some, and the fact that vegetarian diets are generally much lower in fat content. Most adult vegetarians report noticeable weight loss after switching to a vegetarian diet. This weight is usually not regained and as a group vegetarians weigh substantially less than their omnivore peers.[13] To meet only one half of his energy requirements from rice or wheat, a 1-year-old child would have to consume a pound of cooked rice or noodles. Studies in the Orient have shown that small children can consume 20 to 25 g/kg/day of rice at a maximum, quantities that are enormous by Western standards.

Milled wheat products can be tolerated in these amounts but intakes are still larger than we are accustomed to feeding small children. Legumes are no less bulky. Bulkiness may be a problem for adults but it presents the greatest problem for children, whose requirements are higher and whose gastric capacities are less.

Nor is all the energy consumed actually digested. There is a high degree of variability in the energy digestibility of vegetable foods, and this does not always parallel the digestibility of its protein. Although the protein of rice is relatively poorly digested, the starch is very well digested and absorbed, even by infants.[14] The same holds true for milled wheat flour products, such as pasta.[9] In contrast, the carbohydrate in potatoes is less well digested, decreasing substantially the net available energy in the diet and increasing the stool output (G. Lopez de Romaña, MD, G. G. Graham, MD, W. C. MacLean, Jr, MD, unpublished data, December 1979). The same holds true for many legumes. Most of us do not notice these effects of digestibility because the relative contribution of vegetable products to total energy intake of omnivores is much less. In infants who must rely on these foods, however, the effect is often a striking increase in stool weight.

Some of the inadequacy of energy intake can be overcome if fats are eaten in sufficient quantities. Consumption of meat or whole milk automatically carries with it large quantities of fat. Diets devoid of animal protein are low in fat unless exogenous fats are added. In practical terms, this means cooking oils, margarine on rice, noodles or potatoes, or nut butters. As in the case of protein, considerations of the adequacy of energy intake apply to the pure vegetarian, seldom to the lactoovovegetarian or ovovegetarian.

Adequacy of Vitamin Intakes

The major concern in this area is vitamin B_{12}. There is currently no known plant food that contains this vitamin. Vitamin B_{12} is stored in the liver and other tissues. In addition, there is a highly efficient enterohepatic recirculation, resulting in a very small daily turnover. As a result, if initial body stores are adequate, a vegetarian diet can be followed for years by adults without apparent problems. Unless exogenous B_{12} is supplied, however, deficiency is inevitable. This may occur not only in older infants and children but in exclusively breast-fed infants whose mothers are strict vegetarians who shun vitamin supplements.

Vitamin D nutriture is also a potential concern. Fortified milk is one of the main dietary sources for most infants. Egg yolks are also a good source. Although ultraviolet irradiation of 7-dehydrocholesterol on the skin produces cholecalciferol, which is then absorbed and further metabolized to an active form, exposure to sunlight is an unreliable source of the vitamin, especially in north temperate urban areas. In a study in urban and rural Greece, 15% of the infants (nonvegetarians) examined in the winter and spring months had rickets.[15] Nearly all had not received supplementary vitamin D. There was no difference in the prevalence of rickets among those with substantial exposure to sunlight and those with little exposure. Exposure to sunlight cannot be relied on in nontropical areas and since plant foods are poor sources of vitamin D, some source of exogenous vitamin D should be assured.

Both pellagra and beriberi have been related historically to imbalanced and predominantly vegetarian diets. Goldberger showed years ago that the diet common among the poor in the southern United States, namely maize, fatback, and molasses, was pellagragenic. His speculation that a relative deficiency of tryptophan, a niacin precursor, was primarily responsible has since been borne out.[16] Maize has more niacin than human milk but most is bound and not bioavailable unless processed. Tryptophan content is low and total niacin equivalents are about half the amount found in milk. In addition, high leucine intakes from maize may interfere with the conversion of either niacin or tryptophan to nicotinamide adenine dinucleotide, resulting in pellagra.[17] Diets based on maize or sorghum are likely to be pellagragenic, especially in the context of strict vegetarianism.

Dependence on polished rice as the staple food is directly associated with beriberi, making it a potential problem among vegetarians. A high carbohydrate, low-fat diet may increase thiamin requirements.[18] Rice contains adequate amounts of thiamin in the outer layer, most of which is lost in the milling process. The preference of many vegetarians for brown rice should reduce the risk of beriberi. Parboiling is also important in that it reduces the amount of thiamin lost in cooking.

Adequacy of Mineral Intakes

Mineral nutriture has not been recognized as a major problem among vegetarians although some concerns in this area exist. These concerns pertain to the bioavailability of various minerals rather than their actual intakes. Iron is an excellent example. Iron is absorbed from two distinct pools.[19] Heme iron, found in hemoglobin, myoglobin, and ferritin, is animal in origin. Absorption of heme iron is higher than that of nonheme iron and is not affected by other dietary components. In contrast, the absorption of nonheme iron, Fe^{++} and Fe^{+++} inorganic complexes, is highly variable and depends on the foods with which the iron is taken. Two factors known to increase absorption of nonheme iron are the presence of animal protein or ascorbic acid in the diet. Among factors that decrease nonheme iron absorption are phytates and vegetable fiber. The vegetarian often has an intake of iron similar to that of omnivores but none of it is in the more bioavailable form, and the foods consumed diminish the absorption of nonheme iron. Iron nutriture can be a problem even in lactoovovegetarians. Cow milk is a poor source of iron, containing about 1 mg/L. Eggs contain 2 to 2.5 mg/100 g of iron but eggs also tend to inhibit the absorption of nonheme iron.

Bioavailability of calcium, zinc, and copper are negatively affected by diets high in fiber or phytate. It has been calculated that vegetarian diets in some areas of the world contain sufficient phytates to precipitate all the calcium in diet.[20] Oxalates may also form insoluble calcium salts. Both zinc and copper have been mentioned by various authors as potential problems in the vegetarian. As will be seen, these have rarely been a problem in this country.

HEALTH STATUS OF VEGETARIAN CHILDREN

As important as the theoretical nutritional considerations are, the most important question to ask is how well vegetarian children actually fare. Most children in developing countries consume nearly pure vegetarian diets and it is tempting to attribute their poor nutritional status to this fact. This overlooks the heavy burdens of infection to which they are exposed and gives a misleading picture of the nutritional adequacy of the vegetarian diet in a less hostile environment.

Growth

Growth is one of the most sensitive indicators of a child's general health and specifically of his nutritional status. Case reports of poor growth (and other problems) among vegetarians are frequent as they are among omnivores. Few systematic studies of the growth of vegetarian children exist. Shull et al[21] compared the food intake and growth of 72 children younger than 5 years old with established norms. Nearly one half of the children were fed a macrobiotic diet to some degree and one sixth were Seventh-Day Adventists (lactovegetarians). It was difficult in this study to separate completely the data on

zen macrobiotic regimens from those of children consuming more traditional vegetarian diets. Although the lack of well-defined food intake data imposes some limits on the interpretation of the findings, several interesting findings emerged.

When enrolled into the study (mean ages, 30.6 months for girls and 28.7 months for boys), the children weighed less and were shorter than expected from the Harvard reference data. During the studies, gains in weight and length of children younger than 2 years of age were also substandard. The authors speculated that prolonged breast-feeding without appropriate weaning foods might have contributed to this. Growth velocities of children older than 2 years of age approximated the Harvard reference standards. Although at first glance, this appears to be adequate growth these children were already below average for height and weight, so growth should have been above the norm if catch-up were to have occurred. Finally, it was noted that the variability in growth performance was much greater than expected, suggesting that the diet of some children was adequate, that of others quite inadequate.

The only dietary information presented pertained to energy intakes, which were in the range of recommended allowances and did not differ among vegetarian groups. Calculated energy intake and the net available energy after digestion and absorption may differ substantially, however, and the effective energy intake of many of these children may well have been low. In addition, the presence of an unspecified number of lactovegetarians or children fed soy formulas may have improved the apparent growth of the group as a whole, masking more noticeable problems among more strict vegetarians or macrobiotics. Despite these short-comings, this study provides one of the few comprehensive appraisals of growth in vegetarian children and leaves one with the impression that their growth is frequently suboptimal.

Another way to address the question of growth is to follow children whose diets change from pure vegetarian to a less restrictive form. A recent abstract reporting data on an unspecified number of children showed that during a period of approximately two years, height had increased from the fourth to the 41st percentile and weight had increased from the 15th to the 38th percentile when animal protein was added to the diet.[22] Height and weight percentiles attained at the end of the study by these children did not differ from those of siblings who had been lactovegetarians throughout life.

Although the data available are not as complete as one would like, the weight of the evidence is that children with any reasonable amount of animal protein in the diet will more than likely grow normally. A pure vegetarian diet does not seem to preclude optimal growth but the likelihood of this occurring is less. As has been pointed out, however, there may be an association between more strict forms of vegetarianism and a variety of attitudes and life-styles that may adversely affect the growth of the child independent of food intake per se.[2]

Vitamin Deficiency

Most studies of vitamin B_{12} status have been carried out in adults and generally in lactovegetarians. In general, these individuals have been found to have lower serum vitamin B_{12} levels than omnivores although hematological or neurologic evidence of vitamin B_{12} deficiency is lacking.[23,24] A recent abstract comparing complete vegetarians with lactovegetarians and nonvegetarians reported that serum vitamin B_{12} levels were lowest among the strict vegetarians, as would be expected.[25] Several investigators have speculated on the role the colonic flora may play in synthesizing and making vitamin B_{12} available to the strict vegetarian host.

The rapidity with which signs of vitamin B_{12} deficiency can be seen in the rapidly growing infant is illustrated in a recent report.[26] A 6-month-old infant was admitted to the hospital with severe megaloblastic anemia and in coma. Increased pigmentation of the extremities was present. Urinary concentrations of methylmalonic acid and homocystine, both of which require vitamin B_{12} as a cofactor for their metabolism, were increased. This infant had been exclusively breast-fed by a strict vegetarian mother, whose diet had excluded all animal foods and vitamin supplements for eight years. Megaloblastic anemia has also been reported in a breast-fed infant whose mother was a Seventh-Day Adventist.[27] This mother did consume small amounts of animal protein and had taken a multiple vitamin capsule containing vitamin B_{12} during her pregnancy. There seems to be no systematic survey of vegetarian children regarding their vitamin B_{12} status but isolated case reports, such as the aforementioned document, show that the problem is a real one for some infants.

Information concerning vitamin D deficiency and the risk of rickets in these children is somewhat more complete. As part of a survey of the children of new vegetarians, Dwyer et al[28] were able to estimate the vitamin D intake of eight of 17 nearly complete vegetarian children. This averaged 330 ± 229 IU/day (the recommended dietary allowance is 400 IU/day[29]) and was only slightly less than intakes by children consuming less restrictive diets. Nearly two thirds of the children, however, were given supplemental vitamin D on a regular basis. Three of 17 children had intakes of vitamin D of less than 100 IU. Two of eight children for whom data were available had elevated serum alkaline phosphatase values. None of the 17 had clinical signs of rickets.

Mineral Deficiency

Rickets among vegetarians is not confined to young children and is thought in some cases to relate to decreased bioavailability of dietary calcium. Ford et al[30] described eight children of Eastern origin living in England in whom depressed serum calcium concentrations developed between the ages of 9 and 16 years. All eight had been consuming a diet whose staple was chapatis (a traditional Indian flat bread similar to a tortilla) made of whole grain. A seven-week diet trial of a chapati-free diet resulted in an increase of serum calcium levels from 8.4 ± 0.1 to 9.5 ± 0.2 mg/dL. Alkaline phosphatase levels in seven also increased (36 ± 3.5 to 48 ± 6.2 mg/dL). Dent et al[31] have questioned whether binding of calcium by phytates is truly the problem in these children, feeling that adequate vitamin D is more important.

Inadequacy of dietary iron intake has been documented in pure vegetarian children.[32] We are not aware of studies of the prevalence of documented iron deficiency in these children. Similarly, data on zinc and copper are limited. Zinc intakes in adults who are strict vegetarians have not been found to be significantly lower than those of omnivores. Plasma zinc levels appeared to relate to fiber intake rather than to dietary zinc content per se.[33] Severe zinc deficiency with short stature and sexual infantilism has been reported in Iranian and Egyptian children consuming cereal-based diets high in phytates. Concomitant iron deficiency also occurred.[34] To our knowledge, this syndrome has not been seen to date in the United States. Copper deficiency has not been reported in vegetarian children. Since vegetarian diets contain adequate amounts of copper and since copper is so well recycled in the body we would not expect this to be a problem that relates directly to dietary preference.

From the reports of growth, development, and nutritional status, it is clear that while many individual vegetarian children have not fared well, consumption of a strict vegetarian diet does not preclude the possibility of normal growth and development.

An approach to the management of these children to assure optimal growth and development is presented in the next section.

DIETARY MANAGEMENT OF THE VEGETARIAN CHILD

Because dietary restrictions are so variable among vegetarians, it is impossible to produce a set of diet plans suitable for all children. The diet for each child must be worked out using certain general principles. Foremost among these is the recognition that parents who espouse vegetarianism do so in most instances with complete sincerity. Like most parents, they want the best for their children and in this case that means following a set of dietary precepts that they believe facilitate health. The physician must realize that attempts to alter these beliefs radically are unlikely to meet with success. Everyone's time is better spent in assessing the food acceptance and proscriptions of the family and then trying to work out a suitable diet for the child.

Vegetarians are often presumed to have a measure of nutritional sophistication beyond that of the population at large, a presumption that has not been borne out by studies. Consequently, the physician is faced with the problem of educating parents as to the differences in nutrients required to support growth and development in a child as compared with those needed to maintain a fully grown adult. Very likely some alteration of the vegetarian parents' diet willl be necessary to make it suitable for a growing child (omnivore parents similarly make changes). Parents must understand the need for combining cererals with legumes, milk, eggs, or fish if acceptable. A diet that combines several cereals will have variety but will have a severe imbalance of essential amino acids. Even with careful balance, both the parents and the physician should be aware that growth may be slower than expected. Slow growth cannot be equated with poor health and may not be bad per se depending on the degree of retardation. The pediatrician must decide at what point suboptimal growth becomes unacceptable.

From a strictly practical point of view, the physician should try to instill certain dietary practices. Breast-feeding should be the mainstay of the infant's nutrition for at least six months, preferably much longer. Several of the cases cited previously, however, make it clear that careful attention must be paid to the mother's diet in these instances. Among older children, lactovegetarians and lactoovovegetarians will almost certainly do well and the only real concern with these children is the assurance that adequate amounts of milk and eggs are eaten and that the family does not evolve to a more restrictive form of vegetarianism without the physician's knowledge. The lactoovovegetarian needs positive reinforcement, in particular, pointing out the value of dairy products to the child's nutritional well-being.

The critical importance of the cereal-legume paradigm for older children has been previously stressed. In addition, the strict vegetarian child should be changed into a de facto lactovegetarian through the use of soy formulas whenever possible. Formulas made of soy protein isolate with added methionine are nutritionally adequate for the infant who is not breast-fed and for the older child who has been weaned. Soy formulas are usually acceptable to pure vegetarians although some will eschew their use because of the high degree of processing involved in their manufacture. In addition to assuring reasonable protein and energy intakes, commercial soy formulas provide proportional amounts of vitamins and major and trace minerals. In discussing the use of soy formulas with parents, these proprietary formulas should not be confused with homemade soy milks used by some sects. The latter may be no more than the white liquid produced when ground soy beans are soaked and filtered.

A second practical goal for the physician is to gain acceptance by the parents for the use of supplemental vitamins and iron. A sizable part of the requirement of most minerals and vitamins can be supplied by a soy formula but as the child grows older and receives a smaller proportion his total energy intake from formula an additional source of vitamins D and B_{12} and iron must be assured.

Variety in the diet should be stressed. This is especially important from the point of view of complementarity of vegetable proteins. It also relieves monotony and probably helps to maintain adequate food intakes.

Certain foods are not considered safe for infants, however, and are potentially greater problems in some vegetarians. Vegetarians often prefer "natural" foods and may substitute honey for table sugar. The recent reports of botulism in infants fed honey containing botulinus spores but not preformed toxin make this an inappropriate infant food.[35] The tendency to do home canning of fruits and vegetables makes botulism a greater potential concern among vegetarians. Vegetables juices, in particular spinach and carrot, may be inappropriate because of their potentially high contents of nitrites.[36] Many vegetarians consume large quantities of nuts as sources of calcium, iron, and copper. Although nut butters are excellent foods for children, the dangers of aspiration make whole nuts unacceptable. Commercially produced peanut flours contaminated with aflatoxin, a metabolite of *Aspergillus flavus*, have been associated with childhood cirrhosis in India.[37] Crude peanut oils and parboiled rice have also been found to contain the toxin. Aflatoxin has also been linked epidemiologically to Reyes' syndome in Thailand.[38] We are not aware of similar reports in this country.

A final consideration in the care of these children is to try to maintain them in the traditional health care system. Nutritional status is a function of both food intake and infectious or chronic diseases that affect food use. Vegetarian children have a smaller margin of safety in their food intake. Preventive aspects of pediatrics, such as immunization, take on additional importance for them. Because vegetarians as a group tend to shun orthodox medical care, their children are potentially exposed to a variety of untraditional approaches to the treatment of disease, many of which may be harmful. Anything that can be done to minimize this aspect is desirable.

ZEN MACROBIOTICS

Macrobiotic diets are discussed separately for several reasons: it is the philosophy that seems to be espoused by the largest group of new vegetarians. A macrobiotic diet is far more restrictive than pure vegetarianism when the most "desirable" dietary regimen is followed. The most severe cases of malnutrition among infants following unconventional dietary practices seem to have been associated with Zen macrobiotics.

The Zen macrobiotics philosophy is based on the beliefs that Zen Buddhist monks have followed this approach to diet and that they are among the healthiest people in the world. It is difficult to substantiate either of these claims. Zen macrobiotics were introduced into this country by George Ohsawa.[39] There are ten dietary regimens, numbered from −3 to +7. In the progression from lower to higher, desserts, fruits and, later, animal foods are removed from the diet and the percentage of energy from cereals is increased from 10% at level −3 to 100% at level +7. "Cereals" in this case means an exclusive or heavy concentration on brown rice in the diet. Liquid is taken only sparingly.

All foods are given a rating in terms of yin and yang. Brown rice has a value 5 yin to 1 yang (based on the K:Na ratio). Other foods must be eaten in combination, according to their yin or yang value, to maintain the overall dietary ratio at 5:1. Dietary regimens with plus numbers on the scale are generally considered safe. Diets with minus numbers can be indulged in occasionally but are not believed to offer a margin of safety. When beginning the macrobiotic regimen, the adherent is urged to start at level +7 (100% cereal) for several weeks and then add other foods as necessary. In times of illness, a return to the 100% cereal diet is urged. In addition, "industrialized" food and all foods not naturally grown are avoided. Other teachings include the following: body odor comes from animal food; mixed diets create mixed thought processes. In contrast, children require less salt and more water.[40]

The potential nutritional problems for both adults and children increase as one ascends the order of dietary regimens. The lowest five regimens all include foods of animal origin. Game, poultry, and eggs are preferred. Adequate diets for children might be possible at these levels, although 50% of dietary energy is derived from cereals at level 2. At higher levels, the diet becomes more prohibitive than strict vegetarianism and the high percentage of calories derived from cereals combined with the bulk of the diet make it difficult at best to feed children properly. The increasing dependence on rice as a protein source is also dangerous. Supplements of vitamins are shunned. Soy-based formulas are generally unacceptable because they have been processed. A homemade soy-water is used but this is of doubtful nutritional value.

The literature confirms the theoretical disadvantages of macrobiotic diets for children. In the growth study of Shull et al,[21] the growth velocities of these children tended to be less than those of nonmacrobiotic vegetarians. The difference was statistically significant for rates of weight gain between ages 2 and 5 years. In the study by Dwyer et al,[28] calculated intakes of vitamin D by macrobiotic children were 33 ± 67 IU/day compared with 372 ± 267 IU/day by more traditional vegetarians. Physical findings suggestive of rickets were noted only among macrobiotics. Four cases of florid rickets were reported, all in children following macrobiotic regimens.

Nutritional disorders have not been confined to suboptimal growth and rickets. Marasmus and kwashiorkor have been reported by a number of authors, as have scurvy and anemia. A recent report from England emphasizes the inappropriateness of the diet to which macrobiotic infants can be exposed.[41] One infant had been breastfed for four weeks and was then weaned to an "infant food" known as kokoh, a mixture of rice, wheat, oats, beans, and sesame flour. He was admitted to the hospital at 9 weeks of age with poor weight gain, edema, hypothermia, and hyponatremia (serum Na concentration, 114 mEq/L). A second infant had been weaned at 5 months to a diet of kokoh, vegetables, and brown rice. She was admitted to the hospital at 12 months of age with marasmus and rickets. Four malnourished infants of macrobiotic Black Hebrews living in Israel were also recently reported.[42] All had marasmus or kwashiorkor, vitamin B_{12} deficiency, and rickets on admission to the hospital; one died. The authors of both reports were able to negotiate a more acceptable diet for the infants after discharge although a court order was used as a lever in several of the British cases.

All of the potential nutritional problems of pure vegetarianism are concerns for children raised in Zen macrobiotic families, only doubly so. In contrast to vegetarianism, there seems to be no way that a child can remain healthy if a higher level Zen macrobiotic regimen is followed. Furthermore, the parents are likely to be the most zealous of those following unconventional diets. One should try to convince the parents that they should move their child to a lower-order dietary regimen that deemphasizes cereals and allows meat or dairy products. An attempt to supplement the diet with vitamins, especially B_{12}, should be made but the reported experience suggests that this will not meet with great success.

HEALTH FOODS

A brief word about health foods is in order although consumption of health foods is not confined to vegetarians. Many vegetarians, especially Zen macrobiotics, use health foods. The exact definition of health foods is variable but the term usually refers to natural foods, ie, unprocessed foods and so-called organically grown foods.

Food processing has unjustly acquired a bad reputation. As has been mentioned previously, milling or amino acid supplementation may vastly improve the digestibility or quality of vegetable protein. Legumes in particular contain a variety of toxicants and these require processing before they are suitable for consumption. The soaking of beans overnight is an example of one type of traditional processing of legumes. Cooking itself is a form of food processing that vastly improves the digestibility of many foods. With the possible exception of some legumes, the inclusion of unprocessed foods, such as whole grain cereals in the diet, is of no real concern to the older nonvegetarian child who is consuming a normal diet. The decreased digestibility of some natural foods is more than offset by the nutrients available in the rest of the diet. The situation in which natural foods cause concern is in the child who depends on staples for the majority of energy and protein in the diet. The inferiority of digestibility may prove important.

The natural food concept also extends to milk. Some natural food advocates prefer raw unpasteurized milk. Not all raw milk is certified and even when it is there is not absolute assurance that it is free of pathogenic organisms. Control of the quality of raw milk is difficult since it does not pass through centralized dairy processing plants.[43]

Natural vitamin supplements are an important aspect of the natural food movement. Central here is the belief that the naturally occurring form of a vitamin is used better by the body than the synthetic form. The "natu-

ral" nature of most of these products, however, does not stand up to close scrutiny. A favorite is rose hips, with an ascorbic acid content of approximately 2%. The ascorbic acid content is adjusted to about 50% with synthetic ascorbic acid prior to marketing. To do otherwise would require a tablet the size of a golf ball.[44] Similarly, natural B vitamins are yeasts or other food bases highly supplemented with synthetic forms of these vitamins.[44]

Vegetables raised without inorganic fertilizers or pesticides (organic foods), offer no nutritional advantage or disadvantage.[43] It should be pointed out that there are no standards regulating the use of the word organic. There is no guarantee that organic foods are in fact grown in any way differently than most fruits and vegetables. The main drawback to organic foods is their cost. A market basket of 33 foods purchased for $17.49 in a supermarket in 1976 cost 35% to 60% more when bought in health food stores.

CONCLUSIONS

A wide variety of dietary patterns are encompassed by the term vegetarianism. The lactovegetarian or lactoovovegetarian is not a vegetarian in the strictest sense and the diets of these children in many instances will differ little from the usual diet in the United States, with its emphasis on milk consumption. Growth and development can be expected to be normal. Adequate growth in pure vegetarian children is more difficult to achieve. Heavy reliance on soy formula and adequate supplementary iron and vitamins are the nutritional approaches most likely to succeed. In its most strict forms, the Zen macrobiotic diet is inadequate for infants, children, and adults. If the parents are unwilling to retreat to a less restrictive macrobiotic regimen, legal assistance may well have to be sought in the child's behalf.

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References

1. McKenzie J: Profile on vegans. *Pl Fds Hum Nutr* 2:79-88, 1971.
2. Dwyer JT, Mayer LDVH, Dowd K, et al: The new vegetarians: The natural high? *J Am Diet Assoc* 65:529-536, 1974.
3. Joint Food and Agriculture Organization/World Health Organization Ad Hoc Expert Committee: *Energy and Protein Requirements*. WHO Technical Report Series No. 533, FAO Nutritional Meetings Report Series No. 52, Geneva, World Health Organization, 1973.
4. Graham GG, Placko RP, Acevedo G, et al: Lysine enrichment of wheat flour: Evaluation in infants. *Am J Clin Nutr* 22:1459-1468, 1969.
5. Fomon SJ: *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974.
6. Graham GG, Morales E, Placko RP, et al: Nutritive value of brown and black beans for infants and small children. *Am J Clin Nutr* 32:2362-2366, 1979.
7. Graham GG, Placko RP, Morales E, et al: Dietary protein quality in infants and children: VI. Isolated soy protein milk. *Am J Dis Child* 120:419-423, 1970.
8. MacLean WC Jr, Lopez de Romaña G, Graham GG: Protein quality of high-protein wheats in infants and children. *J Nutr* 106:362-370, 1976.
9. MacLean WC Jr, Lopez de Romaña G, Klein GL, et al: Digestibility and utilization of the energy and protein of wheat by infants. *J Nutr* 109:1290-1298, 1979.
10. Eggum BO, Resurreccion AP, Juliano BO: Effect of cooking on nutritional value of milled rice in rats. *Nutr Rep Int* 16:649-655, 1977.
11. Brown KH, Khatum M, Parry L, et al: Nutritional consequences of low dose milk supplements consumed by lactose-malabsorbing children. *Am J Clin Nutr*, to be published.
12. Snyderman SE, Holt LE Jr, Dancis J, et al: Unessential nitrogen: A limiting factor for human growth. *J Nutr* 78:57-72, 1962.
13. Hardinge MG, Stare FJ: Nutritional studies of vegetarians: I. Nutritional, physical, and laboratory findings. *Am J Clin Nutr* 2:73-82, 1954.
14. MacLean WC Jr, Klein GL, Lopez de Romaña G, et al: Protein quality of conventional and high protein rice and digestibility of glutinous and nonglutinous rice by preschool children. *J Nutr* 108:1740-1749, 1978.
15. Lapatsanis P, Deliyanni V, Doxiadas S: Vitamin D deficiency in Greece. *J Pediatr* 73:195-202, 1968.
16. Goldberger J, Tanner WF: Amino-acid deficiency probably the primary etiological factor in pellagra. *Public Health Rep* 37:462-486, 1922.
17. Barakat MR: Pellagra, in Beaton GH, Bengoa JM (eds): *Nutrition in Preventive Medicine*. Geneva, World Health Organization, 1976, pp 126-135.
18. Katsura E, Oiso T: Beriberi, in Beaton GH, Bengoa JM (eds): *Nutrition in Preventive Medicine*. Geneva, World Health Organization, 1976, pp 136-145.
19. Turnbull A: Iron absorption, in Jacobs A, Wormwood M (eds): *Iron in Biochemistry and Medicine*. New York, Academic Press Inc, 1974, pp 370-404.
20. World Health Organization: *Calcium Requirements*, WHO Technical Report Series No. 230, Geneva, World Health Organization, 1962.
21. Shull MW, Reed RB, Valadian I, et al: Velocities of growth in vegetarian preschool children. *Pediatrics* 60:410-417, 1977.
22. Trahms CM: Catch-up growth in children previously deprived of animal protein, abstracted. *Fed Proc* 36:1181, 1977.
23. Smith ADM: Veganism: A clinical survey with observations on vitamin B_{12} metabolism. *Br Med J* 1:1655-1658, 1962.
24. Armstrong BK, Davis RE, Nicol DJ, et al: Hematological, vitamin B_{12} and folate studies on Seventh-Day Adventist vegetarians. *Am J Clin Nutr* 27:712-718, 1974.
25. Register VD, Blankenship JW, Mak JL, et al: Effect of diet on serum, fecal and urinary vitamin B_{12} of total vegetarians, abstracted. *Fed Proc* 36:1121, 1977.
26. Higginbottom MC, Sweetman L, Nyhan WL: A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurologic abnormalities in a vitamin B_{12}-deficient breast-fed infant of a strict vegetarian. *N Engl J Med* 299:317-323, 1978.
27. Lampkin BC, Saunders EF: Nutritional vitamin B_{12} deficiency in an infant. *J Pediatr* 75:1053-1055, 1969.
28. Dwyer JT, Dietz WH, Haas G, et al: Risk of nutritional rickets among vegetarian children. *Am J Dis Child* 133:134-140, 1979.
29. Food and Nutrition Board: *Recommended Dietary Allowances*, ed 8. Washington, DC, National Academy of Sciences, 1974.
30. Ford JA, Calhoun EM, McIntosh WB, et al: Biochemical response of late rickets and osteomalacia to a chupatty-free diet. *Br Med J* 3:446-447, 1972.
31. Dent CE, Round JM, Rowe DJF, et al: Effect of chappatis and ultraviolet irradiation on nutritional rickets in an Indian immigrant. *Lancet* 1:1282-1289, 1973.
32. Trahms CM, Feeney MC: Evaluation of diet and growth of vegan, vegetarian and nonvegetarian preschool children, abstracted. *Fed Proc* 33:675, 1974.
33. Bodzy PW, Freeland JH, Eppright MA, et al: Zinc status in the vegetarian, abstracted. *Fed Proc* 36:1139, 1977.
34. Prasad A: Deficiency of zinc and its toxicity, in Prasad AS (ed): *Trace Elements in Human Health and Disease: Zinc and Copper*. New York, Academic Press Inc, 1976, vol 1.
35. Arnon SS, Midura TF, Damus K, et al: Honey and other environmental risk factors for infant botulism. *J Pediatr* 94:331-336, 1979.
36. Committee on Nutrition: Infant methemoglobinemia: The role of dietary nitrate. *Pediatrics* 46:475-478, 1970.
37. Amla I, Kamala CS, Gopalakrishna GS, et al: Cirrhosis in children from peanut meal contaminated by aflatoxin. *Am J Clin Nutr* 24:609-614, 1971.
38. Olson LC, Bourgeois CH, Cotton RB, et al: Encephalopathy and fatty degeneration of the visera in northeastern Thailand: Clinical syndrome and epidemiology. *Pediatrics* 47:707-716, 1971.
39. Ohsawa G: *Zen Macrobiotics*. Los Angeles, The Ohsawa Foundation Inc, 1965.
40. Abehsera M: *Zen Macrobiotic Cooking*. New York, Avon Books Inc, 1968.
41. Roberts IF, West RJ, Ogilvie D, et al: Malnutrition in infants receiving cult diets: A form of child abuse. *Br Med J* 1:296-298, 1979.
42. Zmora E, Gorodischer R, Bar-Ziv J: Multiple nutritional deficiencies in infants from a strict vegetarian community. *Am J Dis Child* 133:141-144, 1979.
43. Food faddism. *Nutr Rev* 32(suppl):53-56, 1974.
44. Kamil A: How natural are those 'natural' vitamins? *Nutr Rev* 32(suppl):34, 1974.

Nosocomial Pertussis: Possible Spread by a Hospital Visitor

Recently, studies of the epidemiology of pertussis have suggested that young adults with waning immunity and mild illness constitute a major reservoir of infection.[1] Such patients are more commonly the source of exposure to pertussis in children than previously thought. We report an outbreak of nosocomial pertussis involving ten hospital personnel and patients that was traced to the mother of a patient with pertussis. This outbreak underscores the problem of pertussis in young adults and their potential role in the nosocomial spread of this infection.

See also p 521.

The Outbreak.—The organism was introduced into the hospital by a 4-week-old child (patient 1) and her mother, aged 16 years. The mother reported that she had rhinitis and cough eight days after the birth of her child. The child became ill with similar symptoms at about 3 weeks of age, was admitted to an area hospital on Sept 1, 1978, and was transferred to our hospital on Sept 3, 1978.

On admission to the pediatric intensive care unit (PICU), the child was given erythromycin ethylsuccinate and placed in respiratory isolation for the suspected diagnosis of pertussis. Nasal smears for fluorescent antibody (FA) to pertussis were taken from both patient 1 and her mother at the time of admission and were sent by mail to the state health department laboratory. The patient's FA smear was reported as positive within 72 hours; her mother's slides were broken in the mail and the smear was repeated. Although the repeated FA smear was subsequently positive, this was not reported to the house staff immediately, and the mother was not treated with antibiotics until her daughter's discharge from the hospital. During the child's hospitalization, the mother had frequent contact with nursing staff and other patients and visitors in the PICU.

On Sept 20, 1978, the FA smear from a 4-week-old patient in the PICU, taken as part of an evaluation for fever and respiratory distress, was reported as positive. At this time, the infection control program conducted an investigation.

Materials and Methods.—An attempt was made to trace the movements of patients and personnel within the PICU from Sept 3 to 20, 1978. Personnel were interviewed for histories of respiratory illness and to determine the extent of contact with both the patient and her mother during this time. The mother was also questioned regarding her contact with other patients and personnel in the PICU. Nasal smears for pertussis FA and sera for agglutination titers to pertussis were taken from patients, nursing personnel, and pediatric house staff who were present in the PICU from Sept 3 to 20, 1978.

A case of pertussis was defined as the presence of symptoms of rhinitis or cough or nasal congestion and the following: (1) a positive pertussis FA nasal smear; and (2) acute and convalescent sera showing a fourfold increase in pertussis microagglutination titer and absence of a fourfold increase in complement fixation titer to adenovirus, all occurring in a patient or personnel (or a contact of personnel) who had been present in the PICU during this time. Cultures for pertussis were not done.

Results.—In addition to patient 1 and her mother, eight additional cases of pertussis were detected. Six cases in adults were diagnosed: four nurses, the husband of one nurse, and one pediatric house officer. The adults ranged in age from 22 to 36 years (mean age, 23.4 years), and all gave histories of complete immunizations in childhood. The two patients involved were 7 and 16 weeks of age.

When interviewed, the mother reported having had frequent contact with both patients in the beds adjacent to her daughter's. This included holding the children and often assisting in tasks such as feeding them. She also had frequent contact with two of the nurses who subsequently became infected. She remained symptomatic during this time, with nasal congestion and rhinitis, and was not treated with erythromycin until after her daughter was discharged from the hospital on the 22nd hospital day.

Comment.—Natural infection with pertussis is thought to confer long-lasting immunity.[2,3] However, Lambert has reported that protection against pertussis decreases as the interval between vaccination and subsequent reexposure increases.[4] In a community outbreak, an attack rate of 95% was seen in persons who had been vaccinated 12 years or more prior to their exposure to pertussis. In this same study, six of 12 subjects aged 20 years or older who had been completely immunized in childhood contracted pertussis.

In a review of 400 cases of pertussis occurring during the past 18 years, Nelson noted several changes in the epidemiology of this disease.[1] In the six-year period from 1971 to 1977, the incidence of pertussis in children decreased by more than 50%, whereas the number of cases occurring in children less than 12 weeks of age doubled, to 30% of the total. During this period, the most common source of acquisition of pertussis was an adult household contact rather than other children in the household, as in previous years. The present outbreak emphasizes the importance of young adults as a reservoir of pertussis. Indeed, it seems that patient 1 was exposed to pertussis during the first 2 weeks of life, and that her mother was the source of infection.

We believe that this child was not responsible for secondary spread within the hospital since she continued to receive respiratory precautions during the early phase of her illness. In addition, since antibiotics quickly eradicate the organism from the res-

piratory tract without affecting the course of the disease,[5] it would seem likely that the patient's teenaged mother was responsible for infecting not only her daughter but two other patients (patients 2 and 3) and two of the nurses.

Based on other histories obtained from personnel, it seems that one nurse infected her husband and that patients 2 and/or 3 infected the two remaining nurses who "floated" through the unit for only short periods of time. Since the intern who was infected did not provide care for the index patient or have contact with her mother, he was probably infected by a nurse with whom he had worked during his rotation in that unit.

The loss of protection against pertussis and its potential to infect adults has been well demonstrated in two previous nosocomial outbreaks where pediatric patients have been responsible for infection in adult hospital personnel.[6,7] This most recent nosocomial outbreak serves as a reminder that not only does pertussis affect adults but these adults, particularly family members and hospital personnel, may be responsible for nosocomial spread of this disease. The fact that this teenaged mother was initially overlooked as the source of her daughter's infection was probably responsible for spread of pertussis to hospital staff and patients.

Adult household contacts of children with pertussis should be questioned for a history of a recent respiratory illness and should be considered for antibiotic treatment until infection can be ruled out. Moreover, visitors or hospital personnel with any acute respiratory illness should be excluded from patient areas whenever possible. This infection control practice should theoretically minimize transmission of pertussis as well as other respiratory pathogens (eg, influenza, respiratory syncytial virus) to hospital patients and personnel. Such a practice is particularly important on pediatric units where susceptible children often congregate in playrooms and other common areas.

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1. Nelson JD: The changing epidemiology of pertussis in young infants: The role of adults as reservoirs of infection. *Am J Dis Child* 132:371-373, 1978.
2. Linnemann CC Jr, Nasenbeny J: Pertussis in the adult. *Annu Rev Med* 28:179-185, 1977.
3. Pittman M: Pertussis toxin: The cause of the harmful effects and prolonged immunity of whooping cough: A hypothesis. *Rev Infect Dis* 1:401-412, 1979.
4. Lambert HJ: Epidemiology of a small pertussis outbreak in Kent County, Michigan. *Public Health Rep* 80:365:369, 1965.
5. Bass JW, Klenk EL, Kotheimer JB, et al: Antimicrobial treatment of pertussis. *J Pediatr* 75:768-781, 1969.
6. Kurt TL, Yeager AS, Guenette S, et al: Spread of pertussis by hospital staff. *JAMA* 221:264-276, 1972.
7. Linnemann CC, Perlstein PH, Ramundo H, et al: Use of pertussis vaccine in an epidemic involving hospital staff. *Lancet* 2:540-543, 1975.

Nosocomial Pertussis: A Failure of Erythromycin Treatment and Prophylaxis

A variety of antimicrobial agents have been used to treat children with pertussis to decrease the excretion of *Bordetella pertussis* and we hope prevent transmission of the infection to other children.[1-5] Erythromycin is considered the drug of choice for *B pertussis* infections by the American

See also p 520.

Academy of Pediatrics Committee on Infectious Disease because of its low toxicity and superior efficacy in eradicating this organism from the nasopharynx when compared with other antimicrobial agents.[3-7]

We report the failure of seven days of erythromycin therapy to eradicate *B pertussis* from the pharynx of an infant. A second infant who was exposed to this child also contracted pertussis in spite of prophylactic use of erythromycin.

Bacteriologic Methods.—Nasal washing specimens were cultured and examined by direct fluorescent antibody (FA) techniques. Fresh control slides were prepared for each FA examination using stock *B pertussis* and *B parapertussis* cultures. Suggestive colonies of Gram-negative rods growing on modified Bordet-Gengou media were identified as *B pertussis* if fluorescence was 3+ or 4+, control slides stained appropriately, and the organisms failed to grow on chocolate agar.

Report of Cases.—CASE 1.—This 9-week-old, unimmunized female infant was admitted to the hospital after three weeks of rhinorrhea and two episodes of cyanosis and limpness after paroxysmal coughing. During nasal suctioning, she had a respiratory arrest requiring resuscitation with bag and mask.

Her admission WBC count was 21,700/cu mm, with 13% segmented neutrophils, 78% lymphocytes, 5% monocytes, and 4% eosinophils. A nasal washing was negative by direct FA techniques for *B pertussis* but positive by culture.

She was treated with intravenous fluids, humidified oxygen, pertussis immune globulin (human) at 1.25 cc/day intramuscularly for five days, and erythromycin ethylsuccinate at 55 mg/kg/day for seven days. Because of severe life-threatening paroxysms, she was also given hydrocortisone sodium succinate at 30 mg/kg/day intravenously for three days, followed by tapering doses for the next six days. The severity and frequency of paroxysms diminished from 14 per day on day 1 to none on day 9. After seven days of erythromycin therapy, she was taken out of isolation and placed in a seven-bed ward for three days prior to discharge. One day after erythromycin therapy was discontinued, a nasal washing was negative by FA testing. However, the culture from this specimen subsequently had *B pertussis* growth.

She was readmitted five days later because of a mild recurrence of paroxysmal coughing that gradually resolved during the next 14 days. Viral cultures and a repeated nasal washing for *B pertussis* were negative during this admission.

Immediate family contacts were negative by FA techniques and culture for *B pertussis* at the time of the first hospital admission, and all members received five days of erythromycin prophylaxis prior to her relapse.

CASE 2.—This 5-month-old male infant was kept in an open crib 1.83 m away from case 1 for three days after the discontinuation of isolation procedures. He had received only one diphtheria and tetanus toxoids and pertussis vaccine immunization because of a chronic neurological disorder. A nasal washing was negative for *B pertussis* five days after the initial exposure to case 1. He was started on a regimen of erythromycin ethylsuccinate at 55 mg/kg/day at this time, but three days into therapy, he had coryza and a mild cough. The WBC count was 13,600/cu mm, with 27% segmented neutrophils, 29% band forms, 27% lymphocytes, 12% monocytes, and 5% eosinophils. A nasal washing was positive for *B pertussis* on culture.

The coughing became paroxysmal during the next four days, but no cyanosis or complications were noted. This child received an additional eight days of erythromycin therapy prior to discharge, and all symptoms gradually resolved during a two-week period. A repeated nasal washing obtained at the time of discharge was negative for *B pertussis* by both FA techniques and culture.

Results.—Five of the nine infants who shared a room with case 1 had nasal washings obtained five days

after the earliest possible exposure. All five, including case 2, had negative FA and culture results at that time.

Seven infants received erythromycin ethylsuccinate at 40 to 50 mg/kg/day for five days. One infant was receiving chloramphenicol palmitate for *Haemophilus influenzae* meningitis, and one infant did not receive any prophylactic antibiotics. All of the exposed infants were less than 20 months of age, and three infants had not received any immunizations at the time of exposure. The private physicians or parents of all exposed infants were contacted by telephone three weeks after the initial exposure. Only case 2 had respiratory symptoms.

Comment.—The Public Health Service recommends isolation of patients with pertussis "for seven days after the onset of therapy with either erythromycin or ampicillin."[8] However, seven days of erythromycin therapy failed to eradicate *B pertussis* from case 1 and discontinuing isolation led to the transmission of disease to case 2.

Although the number of children studied is small, data from the first patient described here and from other studies suggest that seven days of erythromycin therapy may be inadequate to eradicate *B pertussis* from the nasopharynx. Bass et al have shown that erythromycin was more effective than tetracycline and chloramphenicol in eradicating *B pertussis* from the nasopharynx and that almost all patients had negative cultures after five days of therapy.[4] However, bacteriologic relapses were observed in three of 20 patients treated with tetracycline or chloramphenicol for seven to ten days, and a transient relapse occurred in one of two children treated with erythromycin for ten days. No relapses were observed in patients treated with erythromycin for 14 days by Bass et al or Linnemann et al.[9]

The strain of *B pertussis* isolated from our patients could have been resistant or relatively resistant to erythromycin. Unfortunately, the organism did not survive repeated subculturing, and antibiotic sensitivity testing could not be performed.

It is conceivable that patient 2 could have been infected by someone other than case 1. However, there were no other known cases of pertussis in the hospital, the family members of case 1 were culture-negative, and they also had received erythromycin.

Although several reports have suggested that treatment of individuals exposed to *B pertussis* with erythromycin might prevent infections, we are unaware of any controlled studies.[4,9,10] Case 2 did not receive erythromycin until five days after the earliest exposure to case 1. This delay could have been responsible for the failure of prophylaxis. Since most patients with pertussis are highly infectious for one or more weeks before the diagnosis is made, similar delays in the administration of chemoprophylaxis are likely in other settings. These uncertainties regarding the timing and efficacy of erythromycin chemoprophylaxis only emphasize the point made by Linnemann et al more than five years ago.[11] A large-scale, controlled trial of erythromycin chemoprophylaxis for pertussis is still needed.

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1. Williams S: The value of broad spectrum antibiotics in the treatment of pertussis. *Antibiotics Annu, 1956-1957*, pp 316-318.
2. Medical Research Council: Treatment of whooping cough with antibiotics. *Lancet* 1:1109, 1953.
3. Ames RG, Cohen SM, Fischer AE, et al: Comparison of the therapeutic efficacy of four agents in pertussis. *Pediatrics* 11:323-337, 1953.
4. Bass JW, Klenk EL, Kotheimer JB, et al: Antimicrobial treatment of pertussis. *J Pediatr* 75:768-781, 1969.
5. *Report of the Committee on Infectious Diseases*, ed 18. Evanston, Ill, American Academy of Pediatrics, 1977.
6. Nelson JD: Antibiotic treatment of pertussis. *Pediatrics* 44:474-476, 1969.
7. Bass JW, Crast FW, Kotheimer JB, et al: Susceptibility of *Bordetella pertussis* to nine antimicrobial agents. *Am J Dis Child* 117:276-280, 1969.
8. Center for Disease Control: *Isolation Techniques for Use in Hospitals*, ed 2. US Government Printing Office, 1975.
9. Linnemann CC, Ramundo N, Peristein PH, et al: Use of pertussis vaccine in an epidemic involving hospital staff. *Lancet* 2:540-543, 1975.
10. Altemeier WA, Ayoub EM: Erythromycin prophylaxis for pertussis. *Pediatrics* 59:623-625, 1977.
11. Linnemann CC, Partin JC, Perlstein PH, et al: Pertussis: Persistent problems. *J Pediatr* 85:589-591, 1974.

Adherence of *Staphylococcus aureus* to Infant Nasal Mucosal Cells

Bacterial colonization in the oral cavity of humans is at a low level during the first day after birth and increases to the adult level on the third day.[1,2] The reason for this lack of bacteria during early neonatal life has not been explained. The adherence capacity of groups A and B streptococci to buccal mucosal cells at birth (day 1) is minimal, but it rapidly increases to the adult level on day 3. *Staphylococcus aureus* varies in its ability to attach to nasal epithelial cells.[3] Nasal *S aureus* carriers have greater affinity for *S aureus* than do noncarriers. The epithelial cells of the newborn may serve as a useful tool in further studies of the mechanisms involved in bacterial binding and colonization on mucosal surfaces in man. This colonization is usually requisite for subsequent clinical infection.

The present study investigates the adherence of *S aureus* to nasal mucosal cells in newborns and compares this with the binding capacity of the adult nasal epithelial cells. We chose nasal epithelial cells because the nose is an important reservoir for *S aureus*.

Subjects and Methods.—Healthy infants were selected. Informed consent was obtained from parents after the nature of the procedure or procedures had been fully explained. Nasal epithelial cells were obtained on days 1, 2, 3, 4, and 5 after birth. Corresponding samples were collected from adults for comparisons. Nasal epithelial cells were collected from infants and adults by gently scraping epithelia from the anterior nares with a sterile, wooden applicator by methods previously described.[3]

Staphylococcus aureus was grown in trypticase soy broth, washed three times in phosphate buffer, and resuspended at about 10^8 organisms per milliliter of broth for the adherence experiment. One milliliter each of mucosal cell preparation and bacterial suspension were mixed and incubated at 35 °C for 90 minutes. After incubation, the cells were washed free of unattached bacteria on an 8-μ filter using 40 mL of 0.075M sodium phosphate buffer. Direct smears were prepared from each epithelial cell suspension and stained for 15 s with Gram's crystal violet. The numbers of bacteria adhering to epithelial cells were counted under the light microscope. Control epithelial cell suspensions were incubated with phosphate buffer (without bacteria) to determine the number of bacteria already adhering to the cells.

Results.—Attachment of *S aureus*

Binding of *Staphylococcus aureus* by Nasal Epithelial Cells From Newborns of Various Ages*

Day of Life	Age, hr	N	% of Adherence†	P
1	24 ± 3	10	22.0 ± 10.7	< .001
2	48 ± 4	10	25.0 ± 11.8	< .001
3	74 ± 4	10	38.0 ± 6.8	< .001
4	96 ± 3	5	35.0 ± 7.5	< .001
5	120 ± 4	5	98.0 ± 27.0	> .873

*Fifty epithelial cells were counted for each age group.

†Adherence of *S aureus* to adult nasal mucosal cells was considered 100%. The average ratio of bacteria to epithelial cells was less than 20 during the first four days of life and increased to adult level (40 to 70 bacteria per epithelial cell) on day 5 (120 hr).

to the nasal mucosal cells of infants and adults was compared (Table). The binding of *S aureus* by nasal epithelial cells was markedly less on day 1 ($P < .001$) and remained at a decreased level until day 4 ($P < .001$). On day 5, the *S aureus* binding to epithelial cells reached the adult level. There was no significant difference in adherence of nasal mucosal cells in the adult and the 5-day-old infant ($P > .873$).

Comment.—We have demonstrated that the ability of nasal epithelial cells to bind to *S aureus* is considerably decreased during the first four days of life and reaches adult levels on the fifth day. Ofek et al[1] showed that the binding of buccal epithelial cells to streptococci groups A and B was minimal on days 1 and 2 and reached the maximal level on day 3. The failure of bacteria to adhere to the mucous membrane of newborns may be due to the immature receptor sites or to other local factors in the host because streptococci binding appears to be due to the lipoteichoic acid located on the surface of the organisms.[1,2] Teichoic acid, a component of the *S aureus* cell wall, mediates the binding of these organisms to nasal mucosal cells.[4] Knowledge about the receptor sites for staphylococcal binding on infant epithelial cells is lacking. Nasal colonization of the infant with *S aureus* usually follows staphylococcal colonization of other body sites.[5,6] To our knowledge, the temporal sequence of staphylococcal binding at these other sites has not been investigated to date. It would be of interest to know whether in vitro attachment of the cells from these sites binds *S aureus* earlier than do nasal mucosal cells.

A better understanding of the mechanisms involved in the attachment of *S aureus* to infant nasal epithelial cells should provide useful information regarding colonization of the mucous membranes of newborns. This colonization which is usually requisite for clinical infection of intact skin, occurs in from one third to one half of hospital-delivered infants. The data presented here relate to in vitro introduction of staphylococci to nasal mucosal cells. Extensive study will be required to correlate the extent and ease of staphylococcal adherence to mucosal cells and the frequency of clinical infections.

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Charlene Litz, MS, provided technical assistance.

1. Ofek I, Beachey EH, Jefferson W, et al: Cell membrane binding properties of group A streptococcal lipoteichoic acid. *J Exp Med* 141:990-1003, 1975.

2. Beachey EH: Binding of group a streptococci to human oral mucosal cells by lipoteichoic acid. *Assoc Am Physician Trans.* 88:285-292, 1975.

3. Aly R, Shinefield HR, Strauss WG, et al: Bacterial adherence to nasal mucosal cells. *Infect Immun* 17:546-549, 1977.

4. Aly R, Shinefield HR, Litz C, et al: Teichoic acid in the binding of *Staphylococcus aureus* to nasal epithelial cells. *J Infect Dis*, to be published.

5. Gillespie WA, Simpson K, Tpzer RC: Staphylococcal infection in a maternity hospital. *Lancet* 2:1075-1080, 1958.

6. Hurst V: Transmission of hospital staphylococci among newborn infants: Colonization of the skin and mucous membranes of the infants. *Pediatrics* 25:204-214, 1960.

Corpus Luteum Hemorrhagicum: An Unusual Complication of Anticoagulant Therapy

Hemorrhagic complications of oral anticoagulant therapy are well known. The purpose of this communication is to report an unusual and potentially life-threatening complication of long-term anticoagulant therapy that, as far as we know, has not been previously reported in the pediatric literature.

Report of a Case.—A 17-year-old girl was admitted to the hospital because of a rapidly decreasing hematocrit reading and abdominal pain. She was known to have rheumatic heart disease since age 7 years, and at 13 years of age, her mitral valve was replaced with a Björk-Shiley artificial valve. Postoperatively, she was given daily penicillin G potassium and warfarin sodium. Two months prior to admission, the patient had a transient episode of cerebral ischemia after poor compliance with her warfarin regimen. Her warfarin dose was increased, and she subsequently did well, with prothrombin times that were 2½ times control values. One month prior to admission, she had been hospitalized briefly at another hospital for evaluation of abdominal pain and hematuria that resolved without specific therapy. Prothrombin time was not available.

Four days prior to admission, a prothrombin time was three times the control value, and she was told to temporarily discontinue warfarin therapy. Two days later, she was admitted to another hospital with abdominal pain and vomiting. Hematocrit reading was 32%. Her abdominal pain continued, and her hematocrit decreased to 15%, with no evidence of external blood loss. She was transferred to Children's Hospital of Pittsburgh after receiving a 600-mL transfusion of packed RBCs.

Menarche was at 13 years of age, and regular periods had occurred every four to five weeks without menorrhagia. Her last menstrual period was 2½ weeks prior to admission. She denied sexual intercourse.

On examination, the patient was an obese girl in moderate distress from abdominal pain. The pulse was 116 beats per minute; blood pressure, 120/60 mm Hg without orthostatic change; respirations, 22/min; and temperature, 37.9 °C. The chest was clear. Examination of the heart disclosed the loud opening and closing sounds of the Björk-Shiley artificial valve. A grade 2/6 systolic ejection murmur was heard best at the left sternal border. Diastole was clear. There was diffuse guarding and rebound tenderness in both lower quadrants of the abdomen, without point tenderness, organomegaly, or palpable masses. Pelvic examination showed a normal vaginal introitus, with a normal midposition uterus. No adnexal masses were felt on bimanual examination although there was a fullness in the cul-de-sac on rectovaginal examination. Stool guaiac test was negative. Neurologic examination was normal.

The hemoglobin level was 6.9 g/dL; hematocrit reading was 20%; WBC count was 14,000/cu mm, with 85% segmented forms, 4% lymphocytes, 7% monocytes, and 4% band forms. Radioreceptor assay for human chorionic gonadotropin was negative. Prothrombin time was 20 s, with a control of 11.5 s; partial thromboplastin time was 62 s, with a control of 32 s. Serum electrolytes and BUN levels were normal.

Chest roentgenogram was normal except for the prosthetic valve. Abdominal roentgenogram showed intraperitoneal fluid with calcific densities in the lower abdomen, which were "tooth shaped."

Clinically, intraperitoneal hemorrhage was suspected. The patient's prolonged prothrombin time was corrected by administration of fresh frozen plasma and vitamin K. Her hematocrit reading rapidly stabilized after transfusion with packed RBCs. Within 24 hours, the signs of peritoneal irritation resolved.

An abdominal sonogram showed a large cyst of the left ovary, containing calcium. The patient was given 5,000 units of heparin sodium subcutaneously every 12 hours, and 5 days after admission, she underwent elective surgery. The abdomen contained approximately 600 mL of old blood. A left ovarian cystectomy was performed, removing an intact simple cyst that was found to contain a smaller benign teratoma. Blood was still oozing slightly from a corpus luteum of the right ovary that seemed to be the source of the hemorrhage. No procedure was performed on the right ovary. The patient recovered uneventfully and was restarted on a regimen of warfarin and was given birth control pills containing norethindrone and ethinyl estradiol (Modicon).

Comment.—Minor ovarian bleeding from interruption of ovarian capsule integrity during ovulation is a normal occurrence in young women. Although intracystic and corpus luteum bleeding are occasionally seen in patients receiving anticoagulant therapy, the occurrence of corpus luteum hemorrhage in this group of patients is potentially fatal.[1-8] In most of the reported cases, the diagnosis was not made early, and the patient underwent exploratory laparotomy because of hemorrhagic shock. Our patient's condition was stabilized by rapidly normalizing the prothrombin time and replacing lost blood. Once hemorrhage was controlled, low-dose heparin therapy[9,10] was started to provide anticoagulant protection prior to elective surgery for removal of the ovarian dermoid cyst. At operation, corpus luteum hemorrhage was confirmed.

Although hemorrhagic complications are more commonly seen in patients with a prolonged prothrombin time, massive corpus luteum hemorrhage and even death may occur in patients whose prothrombin times are in the therapeutic range (1.5 to 2.5 times the control values).[8]

Prevention of corpus luteum hemorrhage can be achieved by preventing ovulation. An oral contraceptive was used in the present case. Unfortunately, there are no studies of the effect of birth control pills on patients taking anticoagulants. The relationship between oral contraceptives and venous thrombosis remains controversial. There are increases in measured clotting factors in users of oral contraceptives that are similar to, but less pronounced than, the increases noted with pregnancy.[11] Several studies have suggested that exogenous estrogen treatment or pregnancy are causally related to venous thrombosis and thromboembolism.[12,13] However, a recent review of the subject indicated that claims of an increased risk of venous thromboembolism for patients using oral contraceptives are not justified.[11] We do not wish to ignore the potential risk of thrombosis possibly associated with the use of oral contraceptives or the interaction of oral contraceptives with anticoagulant therapy, potentially complicating management. However, given the current state of understanding, we believe that it is reasonable to use oral contraceptives combined with close monitoring of the prothrombin time in an attempt to prevent recurrence of corpus luteum hemorrhage.

Physicians caring for ovulating adolescents should be aware of potential causes of serious intra-abdominal bleeding related to the reproductive organs. Ectopic pregnancy must be considered and ruled out by appropriate diagnostic tests such as an assay for human chorionic gonadotropin. Corpus luteum hemorrhage in patients taking oral anticoagulants is a potentially fatal occurrence.

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1. Gurewich V, Thomas D: Massive intraperitoneal hemorrhage from a ruptured corpus luteum. *N Engl J Med* 263:909-910, 1960.
2. Weseley AC, Neustadter MI, Levine W: Massive intraperitoneal hemorrhage of ovarian follicular origin during anticoagulant therapy. *Am J Obstet Gynecol* 73:683-685, 1957.
3. Rosenthal AH: Rupture of the corpus luteum, including four cases of massive intraperitoneal hemorrhage. *Am J Obstet Gynecol* 79:1008-1011, 1960.
4. Krause JR, Amores R: Massive intraperitoneal hemorrhage from ruptured corpus luteum during anticoagulant therapy. *South Med J* 69:1220-1221, 1976.
5. Perlman JA, Barnes AB, Demirjian Z: Corpus luteum hemorrhages complicating chronic anticoagulation. *Obstet Gynecol* 49(suppl):20-21, 1977.
6. Wong K, Gillett PG: Recurrent hemorrhage from corpus luteum during anticoagulant therapy. *Can Med Assoc J* 116:388-390, 1977.
7. Lee RA, Kazmier FJ: Ovarian hematoma complicating anticoagulant therapy. *Mayo Clin Proc* 52:19-23, 1977.
8. Semchyshyn S, Zuspan F: Ovarian hemorrhage due to anticoagulants. *Am J Obstet Gynecol* 131:837-844, 1978.
9. Kakkar VV, Field ES, Nicolaides AN, et al: Low doses of heparin in prevention of deep-vein thrombosis. *Lancet* 2:669-671, 1971.
10. Kakkar VV, Corrigan TP, Fossard DP: Prevention of fatal postoperative pulmonary embolism by low doses of heparin: An international multicentre trial. *Lancet* 2:45-51, 1975.
11. Goldzieher JW, Dozier TS: Oral contraceptives and thromboembolism: A reassessment. *Am J Obstet Gynecol* 123:878-914, 1975.
12. Sartwell PE, Masi AT, Arthur FG, et al: Thromboembolism and oral contraceptives: An epidemiologic case control study. *Am J Epidemiol* 90:365-380, 1969.
13. Coon WW, Willis PW III, Keller JB: Venous thromboembolism and other venous disease in the Tecumseh Community Health Study. *Circulation* 48:839-846, 1973.

Eye Involvement in Anaphylactoid Purpura

We have recently observed a patient with an unusually protracted course of anaphylactoid purpura in whom recurrent eye involvement was an unusual feature. Various types of CNS involvement have been uncommonly reported in anaphylactoid purpura.[1-3] However, we have been unable to find a report of recurrent and symptomatic eye involvement in anaphylactoid purpura.

Report of a Case.—A 14-year-old girl had acute multiple joint involvement with swelling of her knees, ankles, and right wrist. At the same time, results of a urinalysis showed microscopic hematuria. Approximately two weeks after the onset of her joint symptoms, numerous small 1- to 2-mm macular lesions were noted on the lower extremities and buttocks. Two weeks later, she had crampy abdominal pain, melena, and gross blood in her stools.

Physical examination at that time showed a pale, irritable girl in moderate distress. A diffuse maculopapular rash was noted, involving the lower extremities and buttocks. Ecchymotic areas developed subsequently within these lesions. Discrete petechial lesions were noted in the same distribution. The petechial lesions in some areas coalesced into purpuric lesions. One isolated purpuric lesion was noted on the forehead. The trunk, abdomen, back, and arms were spared the rash. Pedal edema and erythema of the dorsum of the right foot was present. Examination of her abdomen showed diffuse, moderate tenderness

but no localizing signs and no organomegaly.

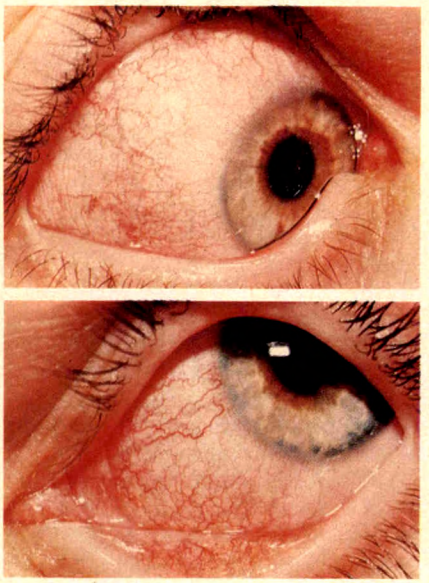
Laboratory studies showed a hemoglobin level of 13.4 g/dL, with a hematocrit reading of 42.2%. The WBC count was 12,000/cu mm, with a normal differential. The platelet count was 295,000/cu mm. The ESR was 12 mm/hr. Urinalysis showed proteinuria (2+), with 50 RBCs per high-power field. No casts were seen in the urinary sediment. A 20-channel automated serum chemistry profile showed no abnormalities. The BUN value was 11 mg/dL, and the serum creatinine level was 0.8 mg/dL. Streptozyme, C-reactive protein, and lupus erythematosus preparation tests were negative. Her β_{1c} globulin level was 72 mg/dL (normal value, 55 to 120 mg/dL). The prothrombin time was 10.8 s, with a control of 11.4 s, and partial thromboplastin time was 30.1 s, with a control of 31.5 s. Serum for anti-DNA antibodies showed less than 1 μg DNA-bound per milliliter.

Eye involvement was first noted approximately five weeks after onset of her joint symptoms and was manifested by photophobia, intermittent pain in the eyes, and eye findings as shown in the Figure. Ophthalmologic evaluation showed deep, vascular engorgement of episcleral vessels in all quadrants of both eyes. There was excessive tearing associated with photophobia. There was no staining of the corneal epithelium, and the anterior chambers were clear. Extraocular movements, pupils, and fundi were all within normal limits. Vision was correctable to 20/20 in each eye. The findings were compatible with a vasculitis involving the vessels of the episcleral region.

The patient's clinical course was marked by severe polyarthralgia, with edema over the joints of the lower extremities. Because of severe joint pain unresponsive to analgesics, corticosteroid therapy was started with prednisone in a dosage of 60 mg daily. During the next six days, there was rapid resolution of her joint symptoms, skin rash, and eye involvement. She was switched to a regimen of prednisone given as a single 60-mg dose on alternate days and a schedule outlined to gradually decrease and then discontinue the prednisone therapy during a period of four weeks.

For the next seven months, the patient's course was one of multiple exacerbations of joint, skin, and eye manifestations whenever her prednisone dose was decreased to less than 30 mg on alternate days. The joint, skin, and eye involvement remained sensitive to daily prednisone administration. All of the nonrenal manifestations resolved within three to five days of reinstitution of daily prednisone therapy. Throughout this time period, she continued to show moderate proteinuria and microscopic hematuria.

Ten months after onset of her disease process, steroid therapy was finally discontinued. During the six-month period after discontinuation of prednisone to the present, she has had three mild episodes of joint pain and eye involvement that was manifested by injection of the scleral vessels and by photophobia. None of these have been severe enough to require reinstitution of steroid therapy and have spontaneously remitted. Her urine remains abnormal, with microscopic hematuria and proteinuria (2 to 3+). However, her BUN and creatinine levels are within the normal ranges for age.



Eye involvement showing right eye (top) and left eye (bottom).

Comment.—Our patient had no history of eye disease other than a refractive error. The temporal relationship of the eye involvement to the other classic findings of anaphylactoid purpura, especially her joint and skin manifestations, suggests that her eye involvement was an integral part of her disease process. This association is also suggested by the prompt resolution of the ophthalmic signs and symptoms with prednisone therapy. The eye manifestations always responded simultaneously with her other symptoms, joint and skin, which were steroid-sensitive. We have been unable to find a previous report of similar ophthalmic involvement in anaphylactoid purpura. Ryder and Marcus[2] have reported a case in which there was transient conjugate eye deviation, cortical blindness, and convulsions associated with anaphylactoid purpura.

Involvement of the CNS with anaphylactoid purpura has been noted as one of the less common manifestations.[1-3] Convulsions have been reported secondary to hypertensive encephalopathy as well as presumed secondary to direct CNS involvement in the disease process.[3] Lewis and Philpott[3] have reported hemiplegia, presumably secondary to cerebral thrombosis or hemorrhage. Additionally, they have reported subarachnoid hemorrhage with uneventful recovery. Our patient has had no other manifestations of CNS involvement during the course of her illness. The basic pathologic process in anaphylactoid purpura seems to be a vasculitis that is characterized by small-vessel involvement with leukocytic perivascular infiltration and thrombosis. An immunologic basis has been suggested by the finding of immunoglobulin, complement, and fibrinogen deposition in capillary walls and connective tissue in skin biopsy specimens taken from affected areas.[4] Similarly, IgA, IgG, IgM and C3 have been noted frequently in the glomerulus of patients with anaphylactoid purpura nephritis.[4,5]

The eye manifestations in our patient are compatible with the basic pathologic process being a vasculitis involving small superficial vessels. Anatomically, the episcleral vessels are similar to the small vessels typically involved in the skin lesions of anaphylactoid purpura. Clinically, the engorgement of the episcleral vessels as well as the symptoms of photophobia and pain were in association with other major manifestations of anaphylactoid purpura such as joint and skin involvement. The prompt resolution of her eye symptoms with institution of daily prednisone therapy is typical of the nonrenal manifestations of anaphylactoid therapy.

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1. Silber DL: Henoch-Schoenlein syndrome. *Pediatr Clin North Am* 19:1061-1070, 1972.

2. Ryder HG, Marcus J: Henoch-Schoenlein purpura. *S Afr Med J* 50:2005-2006, 1976.

3. Lewis IA, Philpott MG: Neurological complications in the Schoenlein-Henoch syndrome. *Arch Dis Child* 31:369-371, 1956.

4. Giangiacomo J, Tsai CC: Dermal and glomerular deposition of IgA in anaphylactoid purpura. *Am J Dis Child* 131:981-983, 1977.

5. Levy M, Broyer M, Arson A, et al: Anaphylactoid purpura nephritis in childhood: Natural history and immunopathology, in Hamburger J, Crusnier J, Maxwell MH (eds): *Advances in Nephrology*. Chicago, Year Book Medical Publishers, 1976, vol 6, pp 183-228.

Letters to the Editor

Chronic 'Diarrhea' and Diet

Sir.—The article by Cohen et al on "Chronic Nonspecific Diarrhea" (JOURNAL 133:490-492, 1979) contains some disturbing concepts and raises important questions.

What is "diarrhea"? What is the normal stool pattern of humans who consume diets rich in fruit and other fibers? The five children reported were receiving diets that in most respects correspond exactly to those recommended as "dietary goals for the United States": increased consumption of complex carbohydrates and "naturally occurring" sugars, from about 28% of energy intake to about 48% of energy intake; reduced overall fat consumption, from approximately 40% to about 30% of energy intake; reduced saturated fat consumption, to about 10% of total energy intake. This is supposed to be accomplished by increased consumption of fruits, vegetables, and whole grains; by decreased consumption of foods rich in total fat, and partial replacement of saturated fats with polyunsaturated fat; by decreased consumption of animal fat, except for young children; by substitution of low-fat and nonfat milk for whole milk, and low-fat dairy products for high-fat dairy products; and by decreased consumption of butter-fat, eggs, and other foods rich in cholesterol. The result of these changes was that, instead of the small, constipated stools typical of developed societies, these children had the more frequent, mushy, sometimes liquid stools that are characteristic of the remaining 90% of the world's population. Despite these changes, the children continued to grow perfectly well. The fact that they did grow at a much better rate than that characteristic of children in developing countries, despite a relatively "low" fat intake, means that the mothers were indeed successful in increasing their intake of the recommended high-fiber, high-complex carbohydrate foods to rather high levels. Is this bad? Is it abnormal? Does it require a work-up for malabsorption? Does everyone in this country have to conform, even in the nature of their stools?

Case 1 was receiving 22% of total calories as fat; case 2 was consuming 25 g of fat per day; case 3 was consuming 16% of total calories as fat; case 4 was consuming 26% of total calories as fat; in the process of being worked up, case 5 was given a "normal" fat intake of 50 g/day, and then the family was counselled to change the family diet to a higher, more appropriate level of fat intake. The fat intakes of these children, when they were being "deprived" of fat, were higher than those of 90% of the world's children.

The wisdom and the scientific validity of the national dietary "goals" are much in debate, but many in the nutrition community believe that there is enough evidence to make it at least prudent to follow the recommendations. Who is to say that the mothers in question were not doing the right thing? And what harm was being done to their children?

The attribution of the frequent, mushy stools to a low fat intake in purely arbitrary. No evidence is put forth to support such a concept. The authors claim that the simple addition of fat to the diet cured the "diarrhea" and that this was accomplished without decreasing the carbohydrate content of the diets. This sounds most unlikely, as the addition of so many fat calories must of necessity have resulted in a decrease in the intake of the high-fiber, high-complex carbohydrate foods. It seems much more likely to me, on the basis of extensive experience with the feeding of such diets, that the high-fiber intake was responsible for the frequent, mushy stools and that its decrease "corrected" these to the normal, constipated stool of our society. In at least two, possibly three of the cases, there were "relapses" when the diet was altered in the direction of higher fiber intakes.

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In Reply.—Dr Graham's interest in and comments on our work are appreciated. As our attention focuses increasingly on diet and other environmental factors that affect disease states, we agree that we must exert great care attributing these relationships to cause and effect. This is particularly important in an era when nutritional data evolve into national policy.

Abnormal bowel movements have been characterized as disease states since the second century AD, when Arataeus described diarrhea as "the discharge of undigested food in a fluid state." Attempts to quantify diarrhea more precisely have met with little success, since "normal" bowel function differs for each person. Even the best index, stool weight, cannot suffice, particularly in cross-cultural comparisons.[1] Thus, one cannot use these measures alone to standardize what is diarrhea and what is not. One must evaluate the change in stool pattern for the individual patient.

The patients described in our report were documented as having diarrhea at the time of presentation as defined by some of the criteria used by Dr Graham and his co-workers[3] ("loose stools of increased number") and by parents of the patients ("when you have to change their socks as well as their diapers"). The stool pattern of these patients after the institution of the dietary regimen was improved to the point of having the fewer and less liquid (soft, semiformed) stools characteristic of normal bowel function. Constipation did not develop in any of the patients.

These chronic diarrheal symptoms may occur in the absence of malabsorption or failure to thrive, because the loss of calories may not be as prominent as the loss of water and solute. Diagnostic and therapeutic measures are obviously important to rule out even more portentious ailments and to appropriately relieve the symptoms (as well as to lessen the laundering of dirty socks).

Chronic nonspecific diarrhea (CNSD) is one of the most common causes of recurrent diarrhea and has been seen both with and without failure to thrive.[4] There is little doubt that it is still a heterologous category of patients with various causes for their symptoms. The pathogenesis of CNSD, and further evidence to implicate fat intake as a major factor and the possible mechanisms of actions, are discussed elsewhere.[5,6] The relationship of dietary fiber and stool

pattern in CNSD is only beginning to be evaluated. Although we did not investigate fiber content in the diets of these patients,[2] we have done so in six subsequent patients with CNSD that responded to our regimen. In those six patients, levels of dietary crude fiber and complex carbohydrates remained the same or actually increased along with the rise in dietary fat content. Where a fall in carbohydrate calories occurred at the expense of the fat increase, the decrease in carbohydrate levels primarily involved monosaccharides and disaccharides. However, there was no consistent pattern in either simple carbohydrate consumption or the relationship of fiber intake to relapse.

Certainly more laboratory and clinical research is needed to elucidate dietary as well as other factors relating to CNSD. At present, chronic recurrent diarrhea continues to be a clinically important syndrome, needing appropriate evaluation and treatment.

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1. Phillips SF: Diarrhea: A broad perspective. *Viewpoints Dig Dis*, November, 1975.
2. Cohen SA, Hendricks KM, Eastham EJ, et al. Chronic nonspecific diarrhea: A complication of dietary fat restriction. *Am J Dis Child* 133:490-492, 1979.
3. MacLean WC, Klein GL, deRomana GL, et al: Transient steatorrhea following episode of mild diarrhea in early infancy. *J Pediatr* 92:562-565, 1978.
4. Lloyd-Still JD: Chronic diarrhea of childhood and the misuse of elimination diets. *J Pediatr* 95:10-13, 1979.
5. Cohen SA, Lake AM, Mathis RK, et al: Perspectives on chronic nonspecific diarrhea: Dietary management. *Pediatrics* 61:808-809, 1978.
6. Cohen SA, Hendricks KM, Laramee S, et al: Chronic nonspecific diarrhea: Dietary relationships. *Pediatrics* 64:402-407, 1979.

Triplo-X and Down Syndrome

Sir.—Gardner in the JOURNAL (133:253-254, 1979) reviewed case reports showing polysomy-X masquerading as Down syndrome.[1] Specifically, persons with XXXX, XXXXX, and XXXXY karyotypes were reported to resemble children with trisomy 21 syndrome. Triplo-X (47XXX) may be added to this list. We have seen a retarded teenage girl who had this karyotype and a suggestive, Down-like facies.[1] A. R. Robinson, MD, pointed out in conversation (November 1979) that children with 47XXX ascertained by newborn screening have also shown an increased incidence of epicanthal folds and clinodactyly, and resemble children with Down syndrome.[2]

Misdiagnosis of polysomy-X is, of course, not the only reason to perform a karyotype on every child with Down syndrome. Approximately 5% of these patients will have a translocation, half of whom have a parent who is a balanced carrier. A karyotype is mandatory for accurate genetic counseling regardless of maternal age.

The term Down syndrome is the nomenclature presently accepted by geneticists, indicating that Dr Down neither had nor owned the condition.

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1. Yeatman GW, Sanders JM: Subtle manifestation of sex chromosome abnormalities in older children and adolescents. Read before a meeting of the American Academy of Pediatrics, San Francisco, Oct 15, 1979.
2. Robinson AR, Lubs HA, Nielson J, et al: Summary of clinical findings: Profiles of children with 47XXY, 47XXX, and 47SYY karyotypes. *Birth Defects* 15:261, 1979.

In Reply.—Major Yeatman adds another clinical example of polysomy-X masquerading as Down's syndrome. The reference to the publication of Robinson et al is welcome, since it had not been published when I did my review. I take exception to Major Yeatman's facetious last sentence concerning the eponym derived from Dr Down's surname. His statement that "... Down syndrome is the nomenclature presently accepted by geneticists..." is inaccurate. The situation is a very mixed one, as indicated by the fact that in journals such as *Clinical Genetics* and the *Journal of Medical Genetics* one sees "Down's syndrome" used, as well as in a genetics textbook such as Levitan and Montagu's *Textbook of Human Genetics*. *The Lancet* is ambivalent: "Down syndrome"[1] appears to be favored now, but it still uses "Burkitt's lymphoma"![2] Eponyms with multiple surnames have never lent themselves to the use of the possessive, such as Prader-Willi syndrome or Laurence-Moon-Biedl-Bardet syndrome. Although writers of stylebooks and committees may issue edicts that eponyms will be used without the possessive, it remains for the spoken language to pass judgment on this. As the Académie Française has found out, the spoken language has a life of its own. If the linguistic mutation "Down syndrome" has survival value, it will be accepted eventually. I will know that time has arrived when the layman says "Bright disease" instead of "Bright's disease."

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1. Alberman E, Berry AC, Polani PE: Planning and amniocentesis service for Down syndrome. *Lancet* 1:50, 1979.
2. Ziegler JL, Magrath IT, Olweny CLM: Cure of Burkitt's lymphoma. *Lancet* 2:936-938, 1979.

Circumcision and Patient Education

Sir.—We read with interest the article on circumcision by Herrera and Trouern-Trend (JOURNAL 133:1069-1070, 1979). Because there are "no medical indications for routine circumcision,"[1,2] counseling parents to ensure informed consent is both difficult and time-consuming. To facilitate counseling, we prepared a handout for parents on newborn circumcision. The literature was extensively reviewed and special efforts were taken to present both the advantages and disadvantages of the procedure. Illustrations, and information on proper hygiene of the uncircumcised penis are also included. The parents are asked to sign a statement indicating that they have read and understand the information provided in the handout. The parents are then counseled by the attending physician. This use of printed educational materials has resulted in a marked reduction in physician time required to ensure informed consent and has also been associated with a 30% reduction in our neonatal circumcision rate.

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1. Committee on Fetus and Newborn: *Standards and Recommendations for Hospital Care of Newborn Infants*, ed 6. Evanston, Ill, American Academy of Pediatrics, 1977, pp 66-67.
2. Committee on Fetus and Newborn: Report of the ad hoc task force on circumcision. *Pediatrics* 56:610-611, 1975.

Books

Pediatric Respiratory Therapy, ed 2, by Marvin D. Lough, Carl F. Doershuk, and Robert C. Stern, 313 pp, Chicago, Year Book Medical Publishers, 1979.

The new, second edition of this volume is a very useful and well-written combination of practical information and advice, with brief summaries of relevant clinical and pathophysiological background information. With contributions by 14 authors, this book should be of most interest to students and practitioners involved directly or indirectly in the respiratory care of children. This edition includes three new chapters and incorporates much of the relevant new understanding, techniques, and equipment that have emerged in five years since the first edition was published.

Development of the cardiopulmonary systems, the pulmonary defense systems, and some nonmetabolic functions of the lung are concisely reviewed in the first two chapters. Some specific diseases and congenital defects that result from or cause abnormalities in these normal patterns are also presented. All the uniquely neonatal clinical, pathophysiological, and therapeutic relevant background information and aspects or respiratory care are contained in chapter 3. A valuable new chapter on pulmonary aspects of cardiovascular disease clearly explains some of the mechanisms by which diseases of the heart and the pulmonary circulation can cause signs and symptoms that are commonly associated with respiratory disease, such as tachypnea and wheezing. Diagrams and tables are effectively used to illustrate the pathophysiology of various congenital heart lesions.

There are three chapters devoted specifically to various aspects of respiratory therapy, which cover such topics as guidelines on organization and administration of a respiratory therapy service, and some practical hints on how to work successfully with children. In addition, the advantages and disadvantages of aerosols, oxygen, intermittent positive pressure breathing (IPPB), different types of mechanical ventilators, and approaches to cleaning respiratory equipment are also discussed. Unfortunately, the authors have avoided any specific mention of the tedious problems involved in effectively cleaning pulmonary function equipment, such as spirometers.

"Diagnostic and Therapeutic Procedures in Pediatric Respiratory Disease" is another new chapter, which contains practical summaries of important aspects of procedures, such as tracheal intubation, thoracentesis, percutaneous lung aspiration, and various radiologic procedures. I disagree, however, with the author's indirect recommendation of oily Dionosil as the "most popular" contrast material for bronchograms, since sterile barium sulfate solution yields excellent results and is less irritating to the respiratory mucosa.

Finally, there are two chapters concerned with pulmonary function testing (including blood gas sampling and exercise testing) in children. The discussion includes hints for obtaining cooperation in young subjects, the effects of growth on lung fuction, and general guidelines for interpretation of test results.

In summary, this is a well-edited, practically oriented book that is highly recommended for pediatric respiratory care practitioners, since it combines concise discussions of appropriately selected clinical, procedural, and theoretical material most relevant to their daily activities. It is generally up-to-date and accurate (there are some minor points I would take issue with, such as the statement that IPPB is effective treatment for pulmonary infection and hypoxia, and the unqualified mention of the use of antibiotic aerosols). The three chapters that are new to this second edition further enhance the value of this most useful publication.

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Ultrasound in Pediatrics, edited by Murray Miskin, K. R. Bloom, B. B. Goldberg, et al, 337 pp, $29.50, New York, Grune & Stratton Inc, 1979.

Ultrasound in Pediatrics is an excellent compilation of the application of ultrasound to five areas in pediatrics. It is not encyclopedic or comprehensive in scope, but in being "directed toward the practitioner of general diagnostic ultrasound, to residents and fellows obtaining training in that specialty and to practitioners of pediatric medicine and surgery," it offers a very useful introduction to this diagnostic method.

The volume is edited by Dr Murray Miskin, who also has contributed the introduction and chapter 6, "Gynecologic Ultrasonography." The other four chapters are contributed by individuals with substantial experience in specific areas of sonography application.

The introduction emphasizes the vast potentiality of ultrasound in the assessment of pediatric patients. "Although no ionizing radiation is used in ultrasonography, it is a modality that introduces mechanical energy into the patient's body" (that is, it is "invasive"), but without deleterious effects at the energy levels utilized. Nevertheless, the designation "noninvasive" is used elsewhere in the book by other contributors and even the editor. The painless feature of ultrasound is a tremendous boon, because the ultrasonographer need not be concerned about inflicting pain on a child and as a result it is easier to get the child to cooperate.

Chapter 2, "Pediatric Sonoencephalography," is the longest of the chapters (152 pages) and the most detailed with 76 figures. It includes applications of A-mode and B-mode methods. In Fig 2-20, a useful graph of ventricular size vs age in 100 pediatric patients is offered. Normal anatomy of the brain and many clinical entities

as manifested by sonoencephalography are described.

Chapter 3, "Pediatric Echocardiography," introduces the recent development of two-dimensional echocardiograms in real time, but the descriptions and figures are via the single crystal examination. The 109 references to this chapter provide comprehensive source material for those especially interested.

Chapter 4, "Abdominal Ultrasound," is also well referenced (91 references) and illustrated (44 figures). The quality of the sonographic pictures is excellent. The chapter includes a section on retroperitoneal structures and to some extent overlaps with chapter 5.

Chapter 5, "Retroperitoneal Ultrasonography," describes useful technical details, some of which are applicable to the abdomen in general. Sonographic images in this chapter are clear and many are correlated with radiologic findings of intravenous urography. Applications of ultrasound in cyst aspiration and in solid lesion biopsy are included.

Chapter 6, "Gynecologic Ultrasonography," follows the format of other chapters in considerations of technique, normal anatomy, and categories of disease. A summary on embryology of the region is offered "to refresh the reader's memory concerning abnormalities that have an embryologic basis."

Ultrasound in Pediatrics is a very useful introductory book that contains a wealth of information in its 337 pages, in its 190 figures containing 397 sonographic pictures, 67 radiologic pictures, 14 drawings, 3 photographic pictures, and 1 graph, and in its three tables. It is a highly recommended addition to pediatric libraries.

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Laryngo-tracheal Problems in the Pediatric Patient, edited by Gerald B. Healy and Trevor J. I. McGill, 129 pp, $13.75, Springfield, Ill, Charles C Thomas Publisher, 1979.

Laryngotracheal diseases of the infant and child can be a potential threat to life, are often difficult to assess, and not infrequently are poorly understood. This book is therefore timely and welcome. It is a slender volume consisting of a series of monographs and two panel discussions by distinguished contributors from the various disciplines of otolaryngology, pediatrics, radiology, anesthesia, and surgery.

The text is introduced with an enlightening discussion of the special anatomical features of the infant larynx that make it so susceptible to obstruction. The middle chapters contain the major body of information so far as the practicing pediatrician is concerned. They deal with the topics of the differential diagnosis of upper airway obstruction, radiological considerations of laryngotracheal problems, inflammatory diseases of the larynx, the team approach to epiglottitis, anesthetic management of epiglottitis, congenital anomalies of the larynx, and subglottic stenosis. These sections are concise, lucid, and comprehensive. The laryngeal photographs and roentgenograms are well done. An unfortunate lapse is the absence of discussion in any of these chapters of foreign bodies lodged in the upper airway.

A following chapter is entitled "Tracheal Considerations in Upper Airway Obstruction." It is an expertly rendered and nicely illustrated treatise on vascular rings. It would have been more comprehensive and closer to its title had some mention been made of congenital tracheal narrowing, laryngotracheal clefts, and tracheoesophageal fistulae. The former condition is rare, and the latter two are not primarily obstructive problems but certainly complicate the newborn airway.

Next is a chapter devoted to respiratory papillomatosis with emphasis on treatment with carbon dioxide laser. This is probably of greatest interest to otolaryngologists with special interest in pediatric airway problems.

The final two chapters are panel discussions dealing with the management of acute inflammatory obstruction and management of artificial airways. They represent the spontaneous comments of the participants and are perforce somewhat discursive and tendentious. Nevertheless, they contain valuable insights of highly experienced clinicians.

The unique appeal of this volume lies in the fact that it successfully collates under a single cover the individual perspectives of all the disciplines involved in the diagnosis and management of diseases that threaten the pediatric airway. It provides valuable guidelines for all charged with the management of this problem and is well worth its modest price.

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Genetic Diseases and Developmental Disabilities: Aspects of Detection and Prevention, edited by Tamah L. Sadick and Siegfried M. Pueschel, 134 pp, $12.50, Boulder, Colo, Westview Press, 1979.

This is a collection of papers presented at the 144th annual meeting of the American Association for the Advancement of Science (AAAS), Feb 13, 1978, in Washington, DC. The state of the art as of that date was reviewed by the following speakers: Barton Childs on genetics and preventive medicine, and genetics and health education; Charles R. Scriver on genetic screening—the heterozygote experience; Robert Guthrie on screening of newborn infants; Richard C. Talamo on screening for α_1-antitrypsin deficiency; Marie Louise E. Lubs on carrier detection in Duchenne's muscular dystrophy and implications for genetic counseling in X-linked disease; Siegfried M. Pueschel on prenatal diagnosis of chromosomal disorders; Aubrey Milunsky (as summarized by Tamah L. Sadick) on prenatal detection of neural tube defects; Maurice J. Mahoney and John C. Hobbins on prenatal diagnosis by fetoscopy and fetal blood sampling; and David G. Nathan on prenatal diagnosis of the hemoglobinopathies. The phrase "developmental disabilities" in the title of the book does not seem very relevant to its contents.

The final chapter of the book, Barton Childs' discussion of genetics and health education, had previously appeared in the *American Journal of Human Genetics* in 1974. As might be expected when papers presented at a meeting are recorded, there is an uneven quality about the book. This is probably unavoidable. Some chapters are finished products, such as those by Childs and by Scriver, and others are in the nature of abstracts. The chapter on prenatal diagnosis of chromosomal disorders is mostly about counseling for amniocentesis and contains little of interest with regard to cytogenetics. Nevertheless, the intent of the AAAS in fostering rapid dissemina-

tion of information is served, even though some presentations seem to be rather rough transcriptions of talks.

Every effort apparently was made to speed publication, as the book was printed by offset directly from the authors' typescript copy. The right margins are not even.

This volume certainly would not be suitable as a textbook devoted to the topics listed earlier, but it does serve to bring to the reader up-to-date current information in certain of the areas listed in the table of contents.

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Feed Your Kids Right, by Lendon Smith, MD, 251 pp, $9.95, New York, McGraw-Hill Book Co, 1979.

This book should not be recommended to patients or their parents. Although many of the statements in the book are based on nutritional evidence, these are counterbalanced by dogmatic pronouncements based on beliefs, half-truths, or untruths.

The casual reader may enjoy some new definitions, eg, antinutrient as a substance that increases the body's need for more nutrients and vitamins, "which are really concentrated foods." Some may enjoy such homilies as "children usually hate vitamins because the B vitamins especially taste like moldy dirt" or "certified raw milk comes from better-fed cows."

Not so amusing or petty, however, are the author's "Five Levels of Health," the apparent basis of his doctrine. These are defined by general activity, irritability, how the child does in school, how the child cuts teeth, and others. Any parents whose child is not absolutely perfect can easily read that they are to blame for feeding the child poorly. Further, if they decide that their child's condition can be placed in one of these five categories, they may well delay diagnosis and treatment while not sparing considerable expense. The recommended use of injections of B complex is mind boggling. The workup for patients who do not get better even after vitamin shots, fasting, and recommendation for psychotherapy is a hair analysis.

In no place in the book can one find data to support the author's unorthodox nutritional approach to disease prevention. The complex stress formula for adrenal support may well have some beneficial effects. However, it would be simpler and less expensive to obtain than by a sugar-free diet (though he allows fructose without explanation), 10 g of vitamin C, vitamin B complex at 200 mg/day, 3 g of pantothenic acid, 500 mg of pyridoxine, 50,000 units of vitamin A, and calcium at 1 g/day. Again, the vitamin C and B complex frequently need be given by injection.

The author's allergy program is similar in many respects to that of Dr William Crook (who has attempted to quantitate effects), such as avoidance of hypoglycemia and foreign substances in the Feingold diet, but its effects are undocumented. The author says it is effective.

Like others who have successfully sold snake oil and cured ill patients, these dicta will work for some. It is estimated that 95% of patients recover regardless of treatment. The author's percentage is probably no lower. The antiscientific and antiacademic approach is best summed up in the author's lack of humility: "biochemistry has now advanced to the state where all the important chemicals needed by the body and present in foods are known." If this is a book of faith, as stated in the final chapter, this should be stated on the flyleaf and at the beginning of the text so that readers are made aware of what they are about to read.

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Bone Dysplasias of Infancy, by Bryan J. Cremin and Peter Beighton, 107 pp, with illus, $39, New York, Springer-Verlag, 1978.

Here the authors have attempted to produce a concise atlas of relevant information concerning bone dysplasias identifiable at birth. They have been moderately successful. Most of the case material is derived from practical experience in the departments of Radiology and Genetics, the University of Capetown Medical School, South Africa. There are 50 figures containing 107 radiographic pictures, 12 clinical pictures, two schematic diagrams, one sonographic picture, and one line drawing. References at the end of each chapter are limited to recent specific articles and general reviews. A short list of other relevant references and monographs is listed in the appendix. The atlas uses both the 1969 and the revised 1977 *Paris Nomenclature for Constitutional Diseases of Bone* for terminology and for chapter arrangement of specific dysplasias. A brief and superficial glossary of useful terms is included. Although the skeletal dysplasias differ widely in their complications and prognoses, they are all heritable conditions with a specific recurrence risk.

The clinical evaluation part of chapter 1 is limited, being only a listing of various dysplasias in degree of lethality and of four clinical features neither consistent nor specific as diagnostic indicators. The statements on genetic evaluation, genetic counseling, and antenatal diagnosis are appropriately basic information. Good schematic diagrams of the mechanisms of autosomal dominant and recessive inheritance are included.

Radiographic techniques are described in chapter 2 under subheadings of "Antenatal Radiology," "Ultrasonography," "Amniography and Fetography," "Postnatal Radiography," "Examination of the Prenatal Radiographs," "Multidisciplinary Evaluation," and "Postmortem Staining Techniques." Noteworthy are the following points. Ultrasonography is preferred for assessment of fetal maturity and position and is capable of detecting gross abnormalities especially in the presence of hydramnios. Radiography is considered the superior diagnostic method for discovering bone dysplasias in the third trimester of pregnancy. Although "multidisciplinary evaluation" is an excellent idea, the authors do not elaborate, but are supportive of the modus operandi of Spranger, a pediatrician, in evaluation of dysplasias: "a. Do not diagnose from a single sign, diagnosis must be made from a pattern; b. Never diagnose from a single site, a skeletal survey is necessary; c. Have patience if you can't make the diagnosis in infancy, the pattern may take time to evolve; d. Lastly, do not publish too early as a single case may only add to confusion."

Chapters 3 to 19 each address a specific dysplastic condition. Noteworthy are the following points. (1) Two types of achondrogenesis have been described, the difference between each being essentially radiological. (2) Thanatophoric dysplasia is the most common form of fetal neonatal

dwarfism and a "cloverleaf" skull may be an associated finding. (3) Patients who survive asphyxiating thoracic dysplasia tend to outgrow the radiographic changes in their long bones and pelves. (4) There are three types of lethal short-rib polydactyly syndrome. Type 3 (Naumoff) is characterized by radiographic signs of severely shortened tubular bones with terminal spurs and a small cranial base. (5) Mesomelic dysplasia, type "Nievergelt," has a distinctive rhomboidal tibia. The authors give concise descriptions of the following dysplasias: chondroectodermal dysplasia, chondrodysplasia punctata, campomelic dysplasia, achondroplasia (most common form of disproportional dwarfism), diastrophic dysplasia, metatropic dysplasia, Kniest syndrome, spondyleopiphyseal dysplasia congenita, Larsen's syndrome, cleidocranial dysplasia, osteogenesis imperfecta congenita, hypophosphatasia, and osteopetrosis and other sclerosing bone dysplasias.

The concise atlas is useful because of its specificity to infancy. It should be a good preliminary reference source for workers in neonatology, pediatrics, genetics, and radiology. For more comprehensive information concerning bone dysplasias, other more detailed sources will be necessary.

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Books in Brief

Combined Cumulative Index to Pediatrics, vol 1 (626 pp, $38, Buffalo, NY, Numarc Book Corp, 1979). Not all journals are in the habit of publishing a cumulative index, so this volume should be of help to those who wish to delve into the recent pediatric literature. Articles published during the years 1976 to 1978 in six American pediatric journals—*American Journal of Diseases of Children, Clinical Pediatrics, Journal of Pediatrics, Pediatric Annals, Pediatric Clinics of North America*, and *Pediatrics*—are listed here by author and by topic. The publishers state that additional volumes are to be forthcoming at three-year intervals, plus an annual supplement for each of the intervening years. The volume, and those promised for the future, should help to make the pediatric bibliophile's task an easier one, though one will have to look elsewhere for articles published in foreign pediatric journals.

Mendelian Inheritance in Man, ed 5, by Victor A. McKusick (975 pp, Baltimore, Johns Hopkins University Press, 1978) (price not stated). This is a complete compilation of human genetic traits and diseases, including anatomic, enzymatic, neurologic, hematologic, and even behavioral abnormalities. The vast number of entries are grouped into the three categories of dominant, recessive, and X-linked conditions. Many are accompanied by a brief discussion, and there are also brief sections devoted to HLA types, to chromosomal assignments for conditions where such is known, and to the increasing list of established enzymatic defects. This book is a most valuable source of information on human genetics. I could not help noting that the JOURNAL ranked high among the list of publications cited as sources for information included in this book.

The Influences of Maternal Hormones on the Fetus and Newborn, vol 5, *Pediatric and Adolescent Endocrinology*, edited by M. Nitzan (286 pp, New York, S Karger AG, 1979) (price not stated, paperback). This volume consists of 14 articles devoted to this general topic, including somatomedin, the sex hormones, catecholamines, prostaglandins, insulin, glucagon, thyroid, adrenal, and pituitary hormones. There is also a chapter about calcium metabolism during pregnancy. Of current interest is the discussion of the role of adrenal glucocorticoids in the maturation of fetal lung biochemistry and function. The role of the "anti-Müllerian" hormone (a hormone produced by the fetal testis, which acts to cause the Müllerian ducts to regress) is also briefly discussed. All in all, this is a fair presentation of current knowledge in this area.

Perinatal Medicine, vol 1 and 2, edited by E. Kerpel-Fronius, P. V. Véghelyi, and J. Rosta (1,449 pp, Budapest, Akadémiai Kiadó, 1978) (price not stated). This is a multiauthored and massive tome that covers the broad and rapidly expanding field of perinatology. The various aspects of this field are presented in considerable detail and, for the benefit of American readers, entirely in English. Prenatal factors, intrauterine diagnosis, circulatory, gastrointestinal, hematologic, metabolic, and infectious factors all receive full attention, as do pulmonary, CNS, and renal phenomena; the approach is truly encyclopedic. One disturbing feature is the all-too-brief account of nutrition.

Intoxications of the Nervous System, part 1, vol 36, *Handbook of Clinical Neurology*, edited by P. J. Vinken and G. W. Bruyn (570 pp, Amsterdam, North-Holland Publishing Co, 1979) (price not stated). One of a series regarding various aspects of neurology, this particular volume is of special interest to pediatricians because of its chapters about lead and mercury poisoning. John Graef writes about lead, reminding us that there are now about 3 million tons of lead smelted or burned each year in the northern hemisphere, which is about ten times the amount used 100 years ago. This chapter about the clinical aspects is followed by one about neuropathology by A. Hirano and M. Iwata (New York), including some striking electron microscopic preparations showing nuclear inclusions, swollen axons, presence of vacuoles, blood vessel damage, and red cell extravasation.

There are three chapters about mercury poisoning. The first two (by D. Marsh, Rochester, NY, and H. Shiraki, Tokyo) deal with organic mercury compounds, the Iraq tragedy of 1972, and Minamata disease in Japan; the third chapter (R. Kark, Los Angeles) deals with inorganic mercury, including acrodynia. Of importance is the fact that though both types of mercury compounds produce CNS symptoms, the spectrum of signs and symptoms differs. Of interest is the failure of observers of children with methylmercury poisoning to describe symptoms and signs of acrodynia. Not all individuals exposed to small amounts of inorganic mercury become ill, and Kark discusses the possibilities of genetic susceptibility and/or dietary predispositions. The remaining chapters are devoted to a variety of intoxicants: arsenic, manganese, mallium, tin, bromide, industrial solvents, methyl alcohol, glucosides, mushrooms, and ergot.

GILBERT B. FORBES, MD
University of Rochester
Medical Center
601 Elmwood Ave
Rochester, NY 14642

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Effective seizure control[1] without cosmetic disfigurement

In 28 studies of patients with mixed grand mal and absence, 76% of all patients gained significant improvement; over one-third became seizure-free. In 60 studies involving pure absence, 86% of patients were improved; half became seizure-free.

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See overleaf for prescribing information

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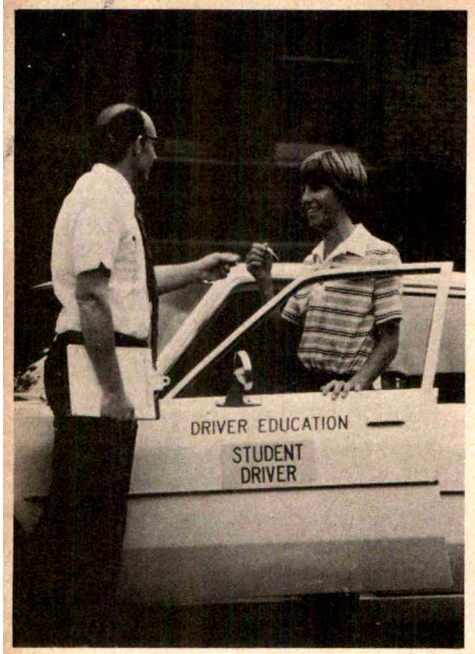

Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported but do not appear dose related. (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increased dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

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In view of the provisions of *The Copyright Revision Act of 1976*, effective Jan 1, 1978, the author(s) of manuscripts, letters to the editor, and book reviews accepted for publication in the JOURNAL will be required to sign and date the following statement: "In consideration of the AMA taking action in reviewing and editing my/our submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to the AMA in the event that such work is published by the AMA."

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All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

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1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 1977; 131:295-296.
2. Koller LR: *Ultraviolet Radiation*, ed 2. New York, John Wiley & Sons, 1965, 141-160.
3. Daughaday WH: The adenohypophysis, in Williams RH (ed): *Textbook of Endocrinology*, ed 5. Philadelphia, WB Saunders, 1974: 31-79.

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NOW PETER

Attention Deficit Disorders* under control...
His natural abilities are coming through

Now Peter's enjoying more things at play as well as in school. He works better with his teacher and classmates... likes doing things with his dad... gets more natural pleasure out of family and friends.

Now that his concentration is improved, his natural abilities are coming through. He's functioning better. Under a well-integrated program of treatment for Attention Deficit Disorders (ADD), hyperactivity and impulsiveness are markedly reduced.

Ritalin (methylphenidate) can be a vital part of his regimen. With adjunctive use of Ritalin, many ADD children are better able to control hyperkinetic behavior —act in a more natural and appropriate manner.

A 20-year record of proven efficacy

Over the years, Ritalin has become an established choice for pharmacotherapy of ADD. In a report by the

BEHAVES MORE NATURALLY.

National Council on Child Health,[1] Ritalin was described as among the most effective and best-documented agents for stimulant therapy in hyperkinetic children.

Reduces hyperactivity, impulsive behavior

Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

Generally well tolerated

Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

*Attention Deficit Disorders: new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

Ritalin . . . only when medication is indicated for Attention Deficit Disorders

Ritalin®
(methylphenidate)
as adjunctive therapy for ADD

Ritalin® C II
(methylphenidate)
Only when medication is indicated

Ritalin® hydrochloride (methylphenidate hydrochloride USP) C II

TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Tablets, 20 mg (peach, scored); bottles of 100 and 1000.

Tablets, 10 mg (pale green, scored); bottles of 100, 500, 1000 and Accu-Pak® blister units of 100.

Tablets, 5 mg (pale yellow); bottles of 100, 500 and 1000.

Dispense in tight, light-resistant container (USP).

665382 C80-14 (1/80)

Consult complete product literature before prescribing

References

1. Kugel RB, Scherz RG, Seidel HM, et al. Council on Child Health: Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4):560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al. Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30**:354-359.
3. MacKay MC, Beck L, Taylor R. Methylphenidate for adolescents with minimal brain dysfunction. *NY State J Med* 1973 (Feb.); **73**:550-554.

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Necrotizing Enterocolitis and Enteral Feeding

Is Too Much Just Too Much?

Ever since Berdon et al[1] and Mizrahi et al[2] characterized neonatal necrotizing enterocolitis (NEC) as a distinct clinical entity, pediatricians have been searching for a unified concept of pathogenesis. Recent reports have attempted to synthesize the multiple factors associated with NEC and have proposed that the critical underlying pathogenic mechanism is either a defect in the integrity of the intestinal mucosal barrier[3] or a primary infectious process.[4]

Goldman, in this issue of the JOURNAL (see p 553), refocuses our attention on the role of enteral feeding and more specifically "overfeeding." In a 13-year review of the experience of one large neonatal unit, he noted that 25 of 26 cases of NEC developed in the three-year period when large feeding volumes (> 150 mL/kg/day) or large daily increases in volume (> 60 mL/kg/day) were the standard practice. When the nursery routine was changed back to limited volumes and restricted daily increments, the incidence of NEC diminished. The concept that enteral feeding may be the primary etiologic factor in the development of NEC has been even more vigorously proposed by Brown and Sweet,[5] who have reported that an extremely restricted feeding schedule has led to all but the disappearance of NEC from their institution.

While Goldman's retrospective epidemiological analysis is of interest, it suffers from all too many of the faults of such studies, namely, poor selection of controls, comparison of nonconcurrent alternative forms of therapy, and reliance on chart data not specifically collected for the study. Of even greater fault is the author's failure to resist the temptation of attributing the development of NEC to a single cause. The most probable pathogenesis of NEC is a complex interrelationship of a triad of factors: disturbed intestinal mucosal integrity, the presence of a critical type and number of bacteria, and a substrate to promote bacterial growth.

A disturbance of the intestinal mucosal barrier appears to be the primary factor in most cases of NEC.[3] This disturbance may be caused by ischemic or hypoxic injury on the basis of vascular insufficiency of the bowel,[2] direct mucosal injury by hyperosmotic feedings,[6] or basic inadequate immunocompetence such as occurs in preterm infants[3] or those deprived of fresh human milk.[4] Lacking an intact mucosal barrier, such a bowel is vulnerable to secondary bacterial invasion. Additionally, as Lifshitz et al[7] have shown, ischemic or hypoxic mucosal bowel injury can predispose to NEC by decreasing mucosal sodium potassium adenosine triphosphatase (ATPase) activity and glucose-galactose transport. The subsequent reduction in carbohydrate transport in the small intestine leads to an increased substrate availability that supports bacterial overgrowth in both the large and small bowel.

Engel[8] has described an NEC-like syndrome in newborn piglets that is accompanied by bacterial invasion of the bowel wall. Histologic data from human tissue usually show similar bacterial invasion.[9] Further evidence of the role of bacteria in the pathogenesis of NEC is that pneumatosis intestinalis or intramural air, the radiologic hallmark of NEC, consists mainly of hydrogen gas, which is derived *only* from bacterial fermentation.[8] In turn, the bacteria that produce hydrogen gas (and that have been associated with NEC) such as *Escherichia coli*, *Klebsiella*, and *Clostridia* sp do so only when presented with a carbohydrate substrate.[8]

Thus, while it is fair to say that feeding appears to be a necessary precondition for bacterial fermentation, hydrogen gas production, and the development of pneumatosis intestinalis, it should be emphasized that pneumatosis intestinalis is only a marker of a phase of the disease process. Furthermore, individual cases of NEC have been reported without evidence of pneumatosis intestinalis.[10-12] What is yet to be proven is that overfeeding itself is the critical variable in the initiation of the necrotizing enterocolitic disease process. Theoretically, overfeeding might support bacterial overgrowth by overwhelming the marginal carbohydrate digestive and absorptive capacity of the immature small bowel and, thus, present substrate for the omnipresent *E coli* and *Clostridia* organisms that colonize the intestine of most neonates within the first 24 hours of age.[4]

Available reported information, however, argues against such a role for overfeeding, despite Goldman's cavalier attempts to dismiss such data. First, although clinical reviews note that over 95% of the infants in whom NEC develops have been fed, there are still reports of NEC developing in the absence of enteral intake.[5,12] Second, in the only controlled study published to date, Book et al[13] showed that two modest rates of increases (10 mL/kg/day vs 20 mL/

kg/day) and a modest maximum of 140 mL/kg/day at 14 and 7 days of age, respectively, did not result either in differences in the incidence of NEC or in the eradication of NEC. Third, recent reports of clustered, epidemic-like cases[4,14] have included infants up to 1 month of age without the classical risk factors previously associated with NEC. These clustered cases emphasize an infectious-type etiology and not a feeding-related etiology. If overfeeding is the primary factor in the development of NEC through its enhancement of bacterial growth and fermentation and hydrogen gas production, one would expect that the radiologic evidence of such, ie, pneumatosis intestinalis, would correlate with the severity and course of the disease process. However, the opposite is all too often the case.[12,15] In fact, as noted, the enterocolitic-necrotic aspect of the disease may occur without any pneumatosis intestinalis.[10-12]

A recent epidemic in our institution illustrates the difficulties in attributing NEC to a particular feeding regimen. Necrotizing enterocolitis developed over a ten-day period in five infants, three of whom were between 17 and 30 days of age. None of the infants had experienced perinatal asphyxia and three had no respiratory distress or indwelling umbilical catheters. Two had only very mild respiratory distress requiring supplemental oxygen and umbilical catheter placement for less than 48 hours. All infants were fed with fresh breast milk or isotonic commercial formulae in amounts not exceeding 150 mL/kg/day. In addition, large daily increases in feedings (> 50 mL/kg/day) did not occur. All these infants were seen initially with severe pneumatosis intestinalis together with portal venous air at least a week after resolution of all respiratory symptoms and institution of feedings. Four of five infants survived without sequelae and one died.

Our experience, as well as other now well-described cluster-like epidemics,[4,14] illustrate the danger in concluding, as Goldman and Brown and Sweet[5] have, that a single change in feeding practice will eradicate or significantly decrease either the incidence or the morbidity and mortality from NEC. Additionally, an overemphasis on the role of enteral feeding and the development of NEC poses the question as to what are the alternatives. Brown and Sweet's[5] recommendations limit caloric intake to levels that are marginal for adequate growth in many growing preterm infants. If their protocol is followed, the inevitable conclusion is that parenteral nutrition with all its known and unknown hazards must be used. If one takes the position that *no* enteral intake should be given in the first week or two of life, when NEC is most common, then one mandates total parenteral nutrition for all such infants with no assurance that NEC will not develop when enteral intake is finally started.

An alternative to restriction of enteral feeding in all preterm infants might be to select, on a clinical epidemiological basis, a particular high-risk group for the development of NEC and restrict their enteral intake. However, there are two problems with this approach. For one, matched studies indicate that the supposed "risk factors" such as low Apgar scores, hypothermia, respiratory distress, hypotension, umbilical catheter placement, or exchange transfusions are not predictive of the development of NEC.[12] In addition, other studies indicate that in 10% to 20% of infants in whom NEC does develop no such "risk factors" were present.[4,16]

What, then, are the options for the clinician? Until more data are available one should not follow Brown and Sweet's[5] dictum and obligate the high-risk preterm infant to limited enteral feeding at a time of possible critical brain growth or subject him inevitably to the risks of parenteral nutrition. On the other hand, one should pay heed to Goldman's experience and limit the enteral intake to reasonable daily quantities and daily rates of increase. Furthermore, in view of the data of Lifshitz et al,[7] when there is the strong possibility of bowel ischemia secondary to prolonged hypotension, presence of a clinically significant patent ductus arteriosus, and/or moderate to severe perinatal asphyxia, enteral feeding should be cautiously introduced, preferably with fresh human breast milk or alternatively with isotonic commercially available formulae. This approach might well reduce the incidence and severity of NEC. Unfortunately, the epidemic-like clusters of cases wherein a particular infectious agent is the primary cause will, regrettably, continue to strike the vulnerable neonate.

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References

1. Berdon WE, Grossman H, Bater DH, et al: Necrotizing enterocolitis in the premature infant. *Radiology* 83:879-887, 1964.
2. Mizrahi A, Barlow O, Berdon W, et al: Necrotizing enterocolitis in premature infants. *J Pediatr* 66:697-706, 1965.
3. Walker WA: Host defense mechanisms in the gastrointestinal tract. *Pediatrics* 57:901-916, 1976.
4. Kleigman RM: Neonatal necrotizing enterocolitis: Implications for an infectious disease. *Pediatr Clin North Am* 26:327-344, 1979.
5. Brown EG, Sweet AY: Preventing necrotizing enterocolitis in neonates. *JAMA* 240:2452-2454, 1978.
6. Book LS, Herbst JJ, Atherton SO, et al: Necrotizing enterocolitis in low-birth-weight infants fed an elemental formula. *J Pediatr* 87:602-605, 1975.
7. Lifshitz F, Wapnir RA, Pergolizzi R, et al: Hypoxia (HY) effects on carbohydrate (CHO) transport. *Pediatr Res* 10:356, 1976.
8. Engel R: Report of the Sixty-eighth Ross Conference on Pediatric Research. Columbus, Ohio, Ross Laboratories, 1975, pp 66-71.
9. Larroche JC: *Developmental Pathology of the Neonate*. Amsterdam, Excerpta Medica, North-Holland Biomedical Press, 1977.
10. Inwood RJ, Hunt CE: Necrotizing enterocolitis, in Raffensperger J (ed): *Swenson's Pediatric Surgery*, ed 4. New York, Appleton-Century-Crofts, 1980.
11. Touloukian RJ: Neonatal necrotizing enterocolitis: An update on etiology, diagnosis and treatment. *Surg Clin North Am* 56:281-298, 1976.
12. Frantz ID, L'Heureux P, Engel RR, et al: Necrotizing enterocolitis. *J Pediatr* 86:259-263, 1975.
13. Book LS, Herbst JJ, Jung AL: Comparison of fast-and-slow-feeding rate schedules to the development of necrotizing enterocolitis. *J Pediatr* 89:463-466, 1976.
14. Guinan M, Schaberg D, Bruhn FW, et al: Epidemic occurrence of neonatal necrotizing enterocolitis. *Am J Dis Child* 133:594-597, 1979.
15. Yu VYH, Tudehope DI, Gill GJ: Neonatal necrotizing enterocolitis: Radiologic manifestations. *Austr Pediatr J* 13:200-207, 1977.
16. Yu VYH, Tudehope DI, Gill GJ, et al: Increasing incidence of necrotizing enterocolitis (NEC): Failure to identify perinatal risk factors. *Pediatr Res* 10:434, 1970.

The Cardiomyopathy of Hypothyroidism Revisited

Are Children Different Than Adults?

Amidst the wide range of social, political, and scientific developments that are presently capturing our attention, the year 1980 will quietly mark the centennial anniversary of the first report of gross anatomical findings in the heart of patients with myxedema by Sir William Ord.[1] The celebration of this event would hardly receive notice in a modern medical journal were it not for a remarkable resurgence of interest in the study of the heart as a target organ for thyroid hormone action. This welcomed new trend results from the creative application of seemingly unrelated advances in the disciplines of endocrinology and cardiology. By combining radioimmunoassay techniques for measurement of thyroid function with the versatility of echocardiography and systolic time intervals as noninvasive tools for the assessment of functional and structural cardiac alterations, investigators are rapidly adding to our understanding of hypothyroid heart disease. The study by Hayford et al in this issue (page 556) is, to our knowledge, the first to apply these techniques to the pediatric age group.

Contrasting with this new trend, the acquisition of knowledge concerning the consequences of thyroid hormone deprivation on the cardiovascular system over the past century was characterized by a relatively slow and controversial pace. The classic "Report of a Committee of the Clinical Society of London nominated December 14, 1883, to Investigate the Subject of Myxeodema"[2] describes the hearts of nine patients dying with myxedema, and the heart was considered abnormal in two patients. In subsequent necropsy studies, the hypothyroid heart has been variously described as pale or "flabby," with normal or dilated chambers, and with or without ventricular hypertrophy. As would be expected, autopsy reports of hypothyroid heart disease have virtually disappeared from the literature in the past two decades.

In 1918, Zondek[3] first suggested that myxedema could lead to disturbances in cardiac function. His concept of "myxedema heart" was subsequently supported by the careful clinical observations of Fahr.[4] For many years thereafter, the findings of enlargement of the roentgenographic cardiac silhouette, slow indolent heart action on fluoroscopy, low voltage of the QRS-complex, flat T waves on the ECG, and distant heart sounds were considered highly indicative of hypothyroid heart disease. Because some of these clinical features were subsequently found to result from pericardial effusions,[5] which frequently accumulates in untreated myxedema, controversy again arose concerning the existence of a true cardiomyopathy in this disorder.

Since the late 1950s, an increasing body of clinical and experimental evidence has gradually accumulated that consistently points toward functional and structural alterations of the heart muscle in untreated hypothyroidism. Low cardiac output, reduced stroke volume, and depressed contractility have been demonstrated by hemodynamic methods in hypothyroid patients.[6,7] Using the technique of systolic time intervals, several investigators studying adult hypothyroid patients documented reduction of the left ventricular ejection time (LVET) and prolongation of the preejection period (PEP).[8,9] These measurements are indirect indices of decreased myocardial contractility and in all reported series were reversed by thyroid hormone replacement. A previously unrecognized echocardiographic pattern of asymmetric thickening or hypertrophy of the interventricular septum, reduced left ventricular internal dimensions, reduced left ventricular outflow tract dimensions, reduced systolic septal excursions, and occasional systolic anterior motion of the mitral valve have been reported in a study of adult hypothyroid patients recently completed at our institution.[10] These echocardiographic features, which at times can completely mimic the pattern of a hypertrophic obstructive cardiomyopathy, were also reversed after thyroid hormone treatment. This unusual finding of a hypertrophic cardiomyopathy in hypothyroidism has been substantiated by autopsy examination of the hearts of three patients dying with uncorrected hypothyroidism.[11]

Within this framework of past controversy and rejuvenated inquiry, the communication by Hayford et al is of importance. To our knowledge, it is the first systematic investigation of the effects of hypothyroidism on the hearts of the young, and these investigators failed to demonstrate significant cardiac impairment in their pediatric patients. The puzzling feature of their study is that the data and conclusions, although derived by similar methodological approaches, are in direct variance with the evidence recently gathered in hypothyroid adults.[8,9] This facet of their article serves clearly to underscore the need for restraint in attempts to extend information obtained in studies of adults to a pediatric population. In the specific case of hypothyroidism, the clinical manifestations of the same pathological process vary widely among different age groups.

RECOGNIZING HYPOTHYROIDISM

In adults, the development of signs and symptoms of hypothyroidism follows a lengthy and insidious course,

with the diagnosis remaining unsuspected for long periods of time. In the elderly, the recognition of hypothyroidism may be masked by neuropsychiatric symptoms that suggest senile dementia, psychosis, or chronic brain syndrome. The ability to date the onset of hypothyroidism in the adult can be accomplished by questioning the patient after full thyroid replacement. In our study of 22 hypothyroid individuals, most patients indicated that their thyroprivic state had been present for four to eight years before diagnosis.[10] One woman, when her condition was fully corrected, insisted hypothyroidism had been present for 16 to 18 years. Hayford et al recognized in their study that dating the onset of hypothyroidism in children is more difficult.

Unlike adults, the diagnosis of hypothyroidism in children is probably made earlier in the course of the disease. Complaints from parents and teachers who compare the affected child with normal siblings or peers alert the physician of the possibility of juvenile hypothyroidism. The physical findings of growth retardation, infantile appearance, and failure in the development of secondary sexual characteristics serve as additional clues to an early diagnosis.

In this context, we would recommend caution in interpreting the data of Hayford et al as an absolute negation of the existence of a cardiomyopathy in untreated hypothyroid children. We perceive their report as additional support to the concept that most of the cardiac consequences of hypothyroidism result not from the severity of thyroid hormone deficiency as reflected by serum concentrations of T_4 and thyroid-stimulating hormone, but from the duration of years in the hypothyroid state. This concept, first proposed by Farh in 1932[12] was clearly substantiated in our adult echocardiographic study aforementioned. In our experience, the severity of cardiac involvement as reflected by the degree of asymmetric thickening of the interventricular septum and compromise of cardiac function correlated better with the duration of the thyroprivic state as assessed by historical documentation, rather than with the degree of hypothyroidism or the absolute values of the thyroid function tests.

CARDIAC FUNCTION

Despite the negative findings presented by Hayford and his colleagues, we believe that abnormalities in cardiac function assessed by systolic time intervals or structural changes detected by echocardiography in the pediatric age group will probably be noted in future studies of older hypothyroid children, if the duration of the thyroprivic state is sufficiently long. It is interesting to note that in Hayford's series the PEP and the PEP/LVET ratio of patient 14, (a 15-year-old) were well above the upper limits of normal for the stated age prior to treatment and clearly returned to normal following thyroid replacement. Unfortunately, the systolic time intervals could not be determined in four of the seven subjects above age 12 in the series of Hayford et al because of technical problems in the echocardiographic tracings. In our series of hypothyroid individuals examined by echocardiography, the youngest patient was a 16-year-old schoolgirl with a bone age of 12 years. Although her interventricular septum measured 11 mm in thickness (the upper limits of normal for an adult), it was well above 7 mm, the upper limits of normal for her chronological age, body surface area, and bone age. In this child, the septal thickness regressed to a normal width after thyroid replacement. We would recommend that future studies of hypothyroid children take into account not only chronological age but also their body surface and, if feasible, their bone age. The latter determination, as well as growth curves, should allow determination of the length of the thyroprivic state.

Mounting experimental evidence points to the heart as being a target organ for thyroid hormone.[13,14] The metabolic derangements caused by thyroid hormone deprivation leading to functional and structural abnormalities demonstrated in adult patients are unknown. The defect may represent a biochemical lesion leading directly to decreased muscle contractility. Alternatively, the accumulation of mucopolysaccharides that has been demonstrated in adult human pathological material,[15] and in experimental animals,[16] may lead to an infiltrative or hypertrophic cardiomyopathy. It is probable that both types of processes are operative in long standing hypothyroidism. Thyroid is not the only hormone to affect the heart. Perturbations in growth hormone[17] and insulin[18] have been shown to lead to a hypertrophic cardiomyopathy in adults and infants, respectively.

Independent of these speculations, the article by Hayford and co-workers wisely emphasizes a frequently forgotten clinical fact. The enlargement of the cardiac silhouette commonly seen in hypothyroidism does not reflect a dilation of the chambers due to a failing myxedematous myocardium, but rather results from the accumulation of pericardial effusion. We agree with their conclusions that simple enlargement of the roentgenographic cardiac silhouette unaccompanied by clinical or echocardiographic signs of cardiac dysfunction should not constitute a deterrent to rapid and appropriate thyroid hormone replacement.

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References

1. Ord WM: Cases of Myxedema. *Trans Clin Soc London* 13:15-22, 1880.
2. Report of a Committee of the Clinical Society of London nominated Dec 14, 1883 to Investigate the Subject of Myxedema. *Trans Clin Soc London* 21:(suppl), 35-46, 1888.
3. Zondek H: Das Myxodemherz. *MMW* 65:1180-1186, 1918.
4. Fahr G: Myxedema heart. *JAMA* 84:345-349, 1925.
5. Kern RA, Soloff LA, Snape WJ, et al: Pericardial effusion: A constant, early and major factor in the cardiac syndrome of hypothyroid-

ism. *Am J Med Sci* 217:609-618, 1949.
6. Graettinger JS, Muenster JJ, Chechie CS, et al: A correlation of clinical and hemodynamic studies in patients with hypothyroidism. *J Clin Invest* 37:502-510, 1958.
7. Amidi M, Leon DF, deGroot WJ, et al: Effect of the thyroid state on myocardial contractility and ventricular ejection in man. *Circulation* 38:229-239, 1968.
8. Hillis WS, Bremmer WF, Lawrie TD, et al: Systolic timer intervals in thyroid disease. *Clin Endocrinol* 4:617-624, 1975.
9. Crowley WF, Ridgway EC, Bough EW, et al: Noninvasive evaluation of cardiac function in hypothyroidism. *N Engl J Med* 296:1-6, 1977.
10. Santos AD, Miller RP, Mathew PK, et al: Echocardiographic characterization of the reversible cardiomyopathy of hypothyroidism. *Am J Med* 68:675-682, 1980.
11. Miller RP, Santos AD, Roth-Moyo L, et al: Hypothyroid heart disease: A reversible obstructive cardiomyopathy. Presented at the 61st annual meeting of the Endocrine Society, June 15, 1979.
12. Fahr G: Myxedema heart: A report based upon a study of 17 cases of myxedema. *Am Heart J* 8:91-101, 1932.
13. Oppenheimer JH: Initiation of thyroid hormone action. *N Engl J Med* 292:1063-1068, 1975.
14. Ciraldi T, Marinetti GV: Thyroxin and Propylthiouracil effects *in vivo* on alpha and beta adrenergic receptors in rat heart. *Biochem Biophys Comm* 74:984-991, 1977.
15. Brewer DB: Myxedema; autopsy report with histochemical observations on the nature of the mucoid infiltrations. *J Pathol Bacteriol* 63:503-512, 1951.
16. Von Knorring J: Analysis of myocardial mucopolysaccharides in hyper and hypothyroid rats and guinea-pigs. *Ann Med Exp Fenn* 48:8-15, 1970.
17. Smallridge RC, Rajfer S, David J, et al: Acromegaly and the heart. *Am J Med* 66:22-27, 1979.
18. Gutgesell HP, Speer ME, Rosenberg HS: Characterization of the cardiomyopathy of infants of diabetic mothers. *Circulation* 61:441-450, 1980.

Regression and Clinical Research

The term *regression* ordinarily suggests some kind of personality or behavior dissolution, when used by physicians or other clinically oriented professionals. A different kind of regression occurs when the clinical geneticist discovers that the sons of tall fathers are not quite as tall, on the average, as their fathers. The sons of short fathers also "regress" toward the population mean, ie, on the average the sons are closer to the mean height of the population than are their fathers. The word "regression" does not have only the behavioral meaning of coming apart or backsliding; it may also mean "recentering" or "reaveraging" in certain interesting clinical situations.

To the statistician, regression may mean several different things. These multiple meanings can confuse the nonstatistician clinician. At least five concepts or associations have an aspect that relates to regression: (1) the *regression line*, depicting the relationship of two variables observed from each element of a sample; (2) the calculations concerned with multiple variables from each element of the sample, often called *multiple regression*; (3) the *filial regression* of characteristics across generations; (4) a form of *regression with correlation*: examination of one set of variables from a sample may show a regression in a correlated set of variables from that sample; and (5) the clustering of repeated sample means around the central value of the population: a *regression of samples* to the universe mean.

A nonmathematical look at each of these forms of regression should help make their occurrence in research reports and in the clinical literature less confusing to nonstatisticians.

REGRESSION LINE

When two measurements on each element of a sample bear a numerical relationship of some systematic sort, the mathematical association may be depicted in a line, called the "regression line." Most researchers are delighted if the line is straight, but statisticians also work with curved or curvilinear regression lines, if such lines best describe the relationship between two variables. Within reasonable boundaries, examples of fairly straight regression lines would be height and arm length, IQ scores and school grades, or hematocrit and hemoglobin measurements.

Several good statistics books[1-4] present the numerical procedures for finding the regression line. Enthusiasm for this kind of regression line exists because it allows the investigator to use one variable to predict another variable. The formulas can tell how accurate such predictions might be, and over what range of values the predictions are valid.

Some statisticians[3] make elaborate distinctions between the regression line, which shows the association between two sets of variables (bivariate regression), and the related concept of correlation of two sets of variables. The regression phenomenon can be expressed in a formula; and, if a line exists for the association of variables, the line can be drawn on a surface. It is often called the "line of best fit."[3] Correlation is a more mathematical concept, tending to show the "tightness of fit" of variables that are more or less correlated with each other.

One author[3] advises that correlation should be used to describe the relationship between variables not under the investigators' control. For example, a correlation might be found between cigarette smoking and lung cancer, both these variables being outside the control of the investigator.

Regression lines, on the other hand, might be used when the investigator can control one of the variables (the independent variable) so as to predict the consequent variable (the dependent variable). An example might be the investigation of pulse rate in response to running at various speeds, controlled by the investigator. A nonbiologic example might be the regression line of caffeine concentration in coffee brewed for various lengths of time.

MULTIPLE REGRESSION

When several variables on each member or element of a sample have a numerical relationship of some systematic sort, the mathematical links may be called "multiple regression" or "multivariate."[1,5] The relationships cannot be shown in a line of two dimensions, because the relationship becomes one of multiple dimensions.[1,5,6] In general, multiple regression techniques have been more widely accepted among researchers in psychology, education, and social sciences, than among those in biology or medicine.

Some authorities in medical research view analysis of multiple variables with considerable skepticism. Feinstein[6] wrote, "Every investigator I have met who uses these techniques either does not fully comprehend the complicated mathematics or has been unable to provide a succinct explanation."

Even in the face of his skepticism, Feinstein gave an interesting example of how analysis of multiple variables might be useful in clinical problems. The development of coronary artery disease (the target variable) might vary in relation to baseline (independent) variables like sex, age, weight, smoking habits, blood pressure, and serum lipid levels. Each of these variables might contribute to a regression line "predicting" coronary artery disease. The line could not be drawn in two-dimensional space, but it could be represented mathematically.

FILIAL REGRESSION

A pioneer in psychological research, Sir Francis Galton, described "filial regression to the mean."[7] This is the drift of offspring toward a general population mean when their parents are known to fall in an extreme tail of a bell-shaped curve. Sons of tall fathers, on average, are nearer the mean height of the general population than their fathers were. Normal parents, from the low tail of the population for IQ, have children with IQ scores that average slightly higher than those of the parents, ie, the children's scores "regress" toward the general IQ mean. This intergenerational kind of regression is sometimes confused with a within-generation "regression" from one attribute to another, as discussed in the next section.

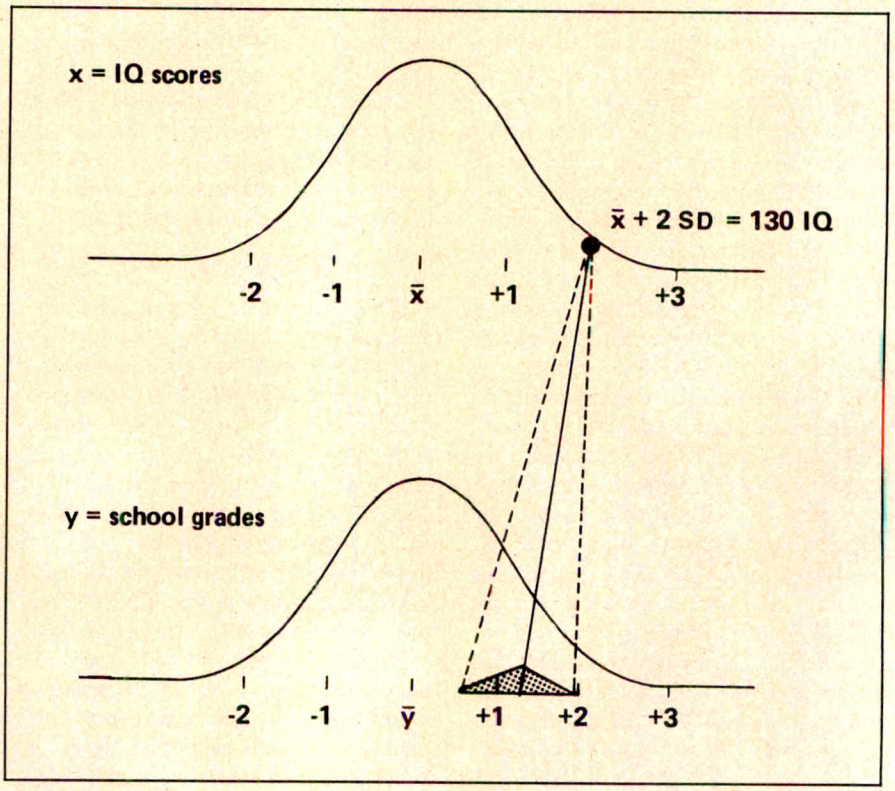
REGRESSION WITH CORRELATION

The filial regression is across generations. It must be distinguished from a different kind of statistical regression across correlated variates from elements of a sample. Let us say, since it is true, that IQ scores are highly correlated with academic grades. If the correlation is high and the calculations are accurate, the educator may find a reasonable estimate of academic potential from IQ scores.

Let us take a look at a subsample of students with IQ scores of 125 to 135 (which would put them about 2 SD above the general population mean IQ of 100). If one looks at the grade point scores for these high-IQ students, these will be, on average, nearer to the population average grade score than their IQ scores are to IQ average; that is, the grade scores may be said to "regress" toward the mean for grades. This relationship is shown in Fig 1. This regression can occur in situations where two measurements of each subject are correlated in a statistical sense. The mathematics of this regression are presented in textbooks of statistics,[5,8,9] although the nonstatistical clinician may be dismayed by the symbolic notations.

The *magnitude* of this kind of regression from one set of variables (IQ) to the other set (school grades) will depend on the results of three calculations: (1) the correlation coeffi-

When two sets of measurements from each element of sample are correlated, subset taken from either tail for one variable will seem to "regress" toward the mean of correlated variable. Magnitude of regression will depend on level of correlation and variance (dispersion) of each set of measurements.[9]



cient between the two sets of measurements; (2) the variance (dispersion, variation) estimated for one variate; and (3) the variance estimated for the correlated variate. For the mathematically comfortable, the formulas and interpretations are presented by Blalock.[1]

CENTRAL TENDENCY REGRESSION

A statistical phenomenon has, in clinical literature,[10] been called "regression to the mean." A few words about sampling theory might clarify this interesting phenomenon.

Samples of large populations (universes) are taken with the expectation that the sample characteristics (called statistics) will provide fair estimates of the universe's characteristics (called parameters). A statistical law says the more clean samples taken from a population, the better the estimates about the dimensions of the universe of interest. (The universe is too large to examine, or one would measure its parameters directly.)

The more samples well studied, and the larger each is, the better the source population can be characterized and its numerical dimensions estimated. As more and more sample averages are determined, the more these averages will cluster, centralize, or regress around the mean of the (impossible to measure) population. In fact, even if the source population (say, weight) is not distributed in a bell-shaped, Gaussian curve (which weights are not), the *averages* of samples will tend to array themselves in a bell-shaped fashion, and the *average of the averages* will be a good estimate of the population mean, becoming better as more samples are averaged.

Where does regression come in? Let us say that a researcher, aware or unaware, selects a sample from either extreme tail of a bell-shaped distribution, then finds the average of that sample. If he takes another sample from that universe, the second sample will likely be found to regress toward the population mean. Even inanimate objects will follow this pattern. If one throws 1,000 dice once, about one in six will turn up with the ace showing; the average score for this subgroup of dice is "1." If those dice that showed the ace are thrown again (a second sample from a universe of dice), they are unlikely to show all aces again; instead, the average score will be some value near the mean score of 3.5. The second sample score has regressed toward the population mean. If one throws samples of dice repeatedly, or even just one die, the averages for each throw (sample) will inexorably centralize (cluster, regress) around the universe mean for dice, or what the statisticians call a *central tendency.*

Some writers make these concepts more obscure than they need to be. For example, McGuigan,[2] in his excellent textbook on research in psychology, wrote, "The regression effect is a statistical artifact that occurs in repeated testings such that the value of the second test score regresses toward the mean of the population."

The tendency of sample means to have a central tendency is not really an artifact; it is a numerical reality of sampling. McGuigan says "repeated testings" when the event is really "repeated sampling." This is a crucial difference, because repeated testing of the same sample will give you results very close to the first testing, with only the random errors of the method causing a change.

One final point should be considered. Even if the first testing is out in an extreme tail of a distribution, there is no absolute assurance that the second sample *must* show a value closer to the population mean; in rare instances the second sample will move even farther out into the tail. It would be more accurate to say that all subsequent samples would have a tendency to cluster around the population mean. If the first sample was from an extreme tail, then the subsequent samples might be said to "regress to the mean" or to show a "regression effect."

As with many situations in clinical research, there are practical aspects that muddy the crystal clarity of numbers. The "central tendency" of multiple samples assumes that the samples are drawn from a relatively homogeneous universe. It would not be appropriate, for example, to lump samples of caffeine measurements from ordinary coffee with caffeine measurements from decaffeinated coffee, just because both universes can be called "coffee." The low caffeine levels in the decaffeinated coffee would not be merely samples from the low tail of a big coffee curve.

This mixing of populations occurs when biology clutters up pure measurement variation. The pattern of laboratory measurements of a substance, say cholesterol, measured repeatedly from a single blood specimen will show a central tendency and a random variation around the central value, depending on the reliability (reproducibility) of the method. In addition, many laboratory procedures contain a second source of error variation, a calibration or standardization error that is nonrandom and may be more in one direction than another. This kind of error may occur when the technician unconsciously favors rounding off instrument readings to the next highest even number; or prefers numbers ending in zero or five over other numbers. (Has any physician ever seen a blood pressure measurement ending in an odd number?)

The random and nonrandom variations due to laboratory techniques are likely to be small in comparison with variation imposed by biology. Accurate measurements of height of the same person will change from morning to night. Body temperatures, hydration, and biochemistry variations change from hour to hour, even in the same person. Add to this the across-individual variations, and the total variance grows apace, even with the best science.

Measuring caffeine in aliquots of coffee from a single cold pot is not the same sampling procedure as measuring caffeine from different pots, some mild, some strong, and some decaffeinated. Each pot will have its own mean, toward which aliquots from that pot will tend to drift.

One challenge to researchers is to distribution. If so, then repeated samples would be expected to tend toward a central value. On the other hand, the sample may look like it is from an extreme tail, but is actually from a separate universe. The serum bilirubin levels of 2-day-old infants are not

simply high tail values from a Gaussian curve of infant bilirubin levels; they are a universe of their own. An IQ of 80 in a child with Down's syndrome is a high tail value for the Down's universe, not a low tail value for normal childhood IQ.

It is risky, as Laskarzewski et al[10] did, to assume that serum lipid measurements for children aged 7 to 14 years are part of the same statistical universe as samples from these children taken four years later, even if the children are called the "same subjects." This assumes that serum lipid values are homogeneous over a broad range of early childhood. The universe of childhood lipid levels may be quite different in its parameters than the universe of adolescent lipid values, even when the same persons are used as subjects.

This is the kind of risk that one takes in concluding that a diastolic blood pressure of 85 mm Hg in a 13-year-old boy is a sample from the high tail of the normotensive universe of youth. In biologic reality, the boy may be in the low tail of a curve from a different universe, one called "hypertensive youth." If the boy is from the normotensive universe, repeated samples of his blood pressure will act as samples from a population with a central tendency much below 85 mm Hg diastolic. His blood pressure will seem to regress toward normal, for in fact the measurements are repeated samples from a normal population. On the other hand, if he is a member of the universe called hypertensive, repeated samples of his blood pressure will cluster to the mean for that population, perhaps around 95 to 100 mm Hg diastolic.

This biologic uncertainty about whether a sample is from an extreme tail of a distribution dictates the use of control groups. By using controls, the possibility of regression to some unknown mean (central tendency) is evenly balanced across the treated and the untreated. This allows the effect of treatment or intervention to be distinguished from the tendency for samples to drift toward their population mean.

Biology does another ugly thing to some sample measurements: it allows some measurements to vary in one direction but not in the other. Children can grow taller, but not shorter. We rarely see body temperatures 3 °C below 37 °C, but we often see temperatures 3 °C above normal. Blood glucose levels can only fall about 100 mg/dL below normal, but they can rise several multiples of that above normal.

Schor[11] wrote that all the flies in a closed room might be on the ceiling at 8 AM; but at some point in the following 24-hour period, more of them would be below the ceiling than above it. This nicely portrays the difference between biology and pure random variables. In biology, the room may be closed and the flies restricted to staying on the ceiling or below it. In a random universe, the flies would be allowed random movement; so that at some subsequent time, there could be just as many flies above the ceiling as below it. Schor's parable reminds us to be on guard about the purity of unencumbered numbers (remember those dice), in contrast with the sometimes muddy and perverse variables of biological and other dynamic systems.

McGuigan[2] points out an interesting variant on the central tendency (regression) phenomenon. He discusses the "interrupted time series." An observer may select the highest recent value of a time sequence of values as a baseline, rather than finding the true baseline over the entire series. Selecting a recent extreme value makes it likely that the next point on the time sequence curve will be closer to the baseline of the entire sequence. McGuigan used the example of highway traffic deaths. The researcher chose the latest and highest value in a time sequence curve for traffic death rates, then attributed a subsequent fall in the death rates to the intervention of a traffic safety program. Rainfall measurements are likely to drift toward the average rainfall, after a record high rainfall. Beware of data in a time series that follow closely after a series high or a trough.

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References

1. Blalock HM Jr: *Social Statistics*, ed 2. New York, McGraw-Hill Book Co Inc, 1979.
2. McGuigan FJ: *Experimental Psychology*, ed 3. Englewood Cliffs, NJ, Prentice-Hall Inc, 1978.
3. Schefler WC: *Statistics for the Biological Sciences*, ed 2. Reading, Mass, Addison-Wesley Publishing Co, 1979.
4. Leaverton PE: *A Review of Biostatistics*, ed 2. Boston, Little Brown & Co, 1978.
5. Cohen J, Cohen P: *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. New York, John Wiley & Sons Inc, 1975.
6. Feinstein AR: Clinical biostatistics: XXI. A primer of concepts, phrases, and procedures in the statistical analysis of multiple variables. *Clin Pharmacol Therap* 14:462-477, 1973.
7. Vernon PE: *Intelligence: Heredity and Environment*. San Francisco, WH Freeman & Co, 1979.
8. Davis CE: The effect of regression to the mean in epidemiologic and clinical studies. *Am J Epidemiol* 104:493-498, 1976.
9. Ederer F: Serum cholesterol changes: Effects of diet and regression toward the mean. *J Chronic Dis* 25:277-289, 1972.
10. Laskarzewski P, Morrison JA, deGroot I, et al: Lipid and lipoprotein tracking in 108 children over a four-year period. *Pediatrics* 64:584-591, 1979.
11. Schor SS: The floor-and-ceiling effect. *JAMA* 207:120, 1969.

Feeding and Necrotizing Enterocolitis

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• **Twenty-six infants had necrotizing enterocolitis (NEC) in the neonatal unit of the Long Island Jewish-Hillside Medical Center, New Hyde Park, NY, between 1964 and 1976; 25 of these cases occurred between 1973 and 1976. The relationship of feeding practices to this clustering of NEC cases was investigated in two ways: (1) A 10% sample of all admissions, 1964 to 1976, was studied. A striking correlation was found between the yearly incidence of NEC and the percentage of infants in that year who had received large increases in daily feeding volume. The highest mean daily feeding volume occurred in 1974 and 1975, the two years of peak NEC incidence. (2) The feeding records of the 26 NEC cases were studied. Thirteen NEC patients had had large increases in feeding volume within two days of NEC onset. Seven others received > 150 mL of formula per kilogram per day prior to NEC onset. Rapid increase in feeding volume and the use of large volumes are suggested as important etiologic factors of NEC.**

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Necrotizing enterocolitis (NEC) was virtually unknown in the neonatal unit of the Long Island Jewish-Hillside Medical Center (LIJHMC) during the 1960s and early 1970s. In the mid 1970s, concurrent with a change in feeding policy, the incidence of NEC increased dramatically. The present study was designed as an epidemiologic investigation of the relationship between feeding practices and NEC in the neonatal unit of our hospital.

MATERIALS AND METHODS

The study consists of three parts: (1) determination of the incidence of NEC during the period from 1964 to 1976; (2) determination of the feeding practices and their variation during this time period; and (3) determination of the feeding practices in the group of infants with NEC.

The study was limited to infants admitted to the neonatal unit between Jan 1, 1964, and Dec 31, 1976. Only infants with birth weights less than 2,500 g were included.

Standardized methods were used for case findings and standardized criteria were adopted for the diagnosis of NEC. Three methods were used for case finding:

1. Face sheet diagnosis: All charts with a face sheet diagnosis of necrotizing enterocolitis, enteritis, or colitis were reviewed. A case was accepted as NEC if there was definite roentgenographic evidence of pneumatosis plus two or more of the following: (*a*) vomiting; (*b*) abdominal distention; and (*c*) grossly bloody or guaiac-positive stools.

2. Deaths: The charts of all infants dying after the second day of life were reviewed. A case was accepted as NEC if an autopsy showed pathological findings of NEC or, if no autopsy was done, the case fulfilled the criteria for face sheet diagnosis.

3. Abdominal surgery: The charts of all infants subjected to abdominal surgery (other than herniorraphy) were reviewed. A case was accepted if there were pathological findings of NEC.

The chart of every tenth admission to the neonatal unit between Jan 1, 1964, and Dec 31, 1976, with birth weight less than 2,500 g was reviewed. The total volume of feeding received by the infant during each 24-hour period was recorded for each of the first 14 days of life. This value was divided by the current weight of the infant to yield the daily feeding volume in mL/kg. Differences between the daily feeding volumes for adjacent days were calculated and recorded as the daily feeding volume increase in mL/kg.

The daily feeding volume and the daily feeding volume increase were calculated and recorded for each infant with NEC on every day of life up until the infant was taken off feedings because of NEC symptomatology. All statistical analyses were carried out by calculation of χ^2 with Yates' correction.

RESULTS

A total of 26 cases of NEC were found. Only one occurred prior to 1973, with the remaining 25 clustered in the period from 1973 to 1976. The increased incidence for 1973 to 1976 is not accounted for by the numbers of admissions or survivors (Fig 1). The percentages of infants less than 1,500 g in birth weight were 29.8 in the years 1964 to 1972 and 27.6 in the years 1973 to 1976. The percentages of infants born elsewhere and transported to the neonatal unit were 54.8 in the 1964 to 1972 period and 61.1 in the 1973 to 1976 period.

The mean daily feeding volumes in the seventh and 14th days of life, based on the 10% sample, are given in Table 1. The highest daily feeding volumes on the seventh day occurred in 1974 and 1975, the two years with the highest incidence of NEC.

The percentage of infants who received one or more large daily feeding volume increases (> 40 or 60 mL/kg/day) is shown in Fig 2. The figure reveals a striking parallelism between the incidence of NEC and large jumps in feeding volume.

The percentage of infants in whom feedings were delayed for more than two days is as follows: 1964 to 1968, 15%; 1969 to 1972, 12%; and 1973 to 1976, 24%. A larger percentage of the infants had delayed feedings during the most recent period (1973 to 1976), possibly reflecting the use of respirators.

The data for feeding volumes in the 26 cases of NEC are given in Table 2. Twenty of the infants (77%) were receiving more than 100 mL/kg/day immediately prior to the onset of NEC. Fifteen of the 26 infants (57%) had received one or more large daily feeding volume increases (> 60 mL/kg/day) prior to the onset of NEC. This proportion is significantly higher than the 15% incidence of such large daily increases in the 13-year period from 1964 to 1976 ($P < .0001$), and it is also significantly higher than the 29% incidence of such large increases during the four-year period from 1973 to 1976 when all but one case of NEC

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Table 1.—Mean Daily Feeding Volumes

Year	Day 7	Day 14
1964	117	164
1965	114	162
1966	114	162
1967	93	156
1968	106	157
1969	93	164
1970	83	148
1971	99	155
1972	90	152
1973	117	159
1974	136	168
1975	139	178
1976	105	183

Table 2.—Maximal Volume and Rate of Increase Prior to NEC*

mL/kg	No. of Infants	% of Group
Maximal Daily Feeding Volume		
0-50	1	4
51-99	5	19
100-149	8	31
150-199	10	38
200-249	2	8
Maximal Daily Feeding Volume Increase		
0-19	1	4
20-39	7	27
40-59	3	12
60-79	10	38
80-99	5	19

*NEC indicates necrotizing enterocolitis.

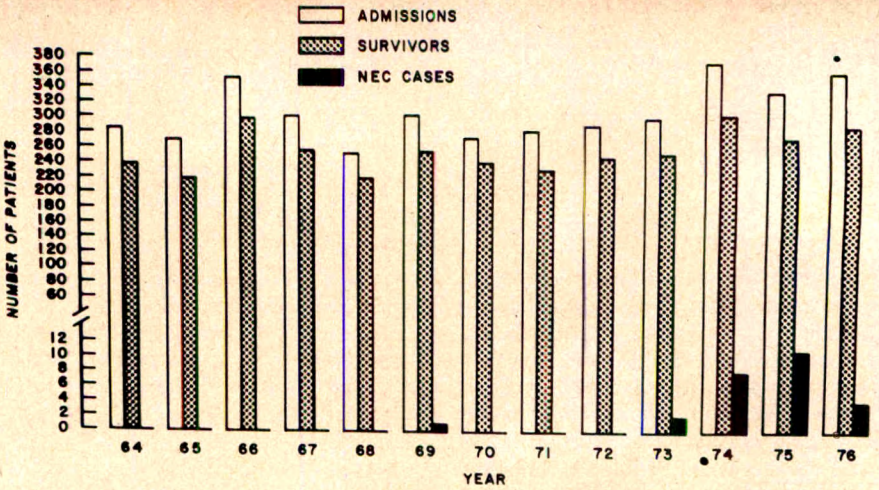

Fig 1.—Numbers of admissions, survivors, and cases of necrotizing enterocolitis (NEC).

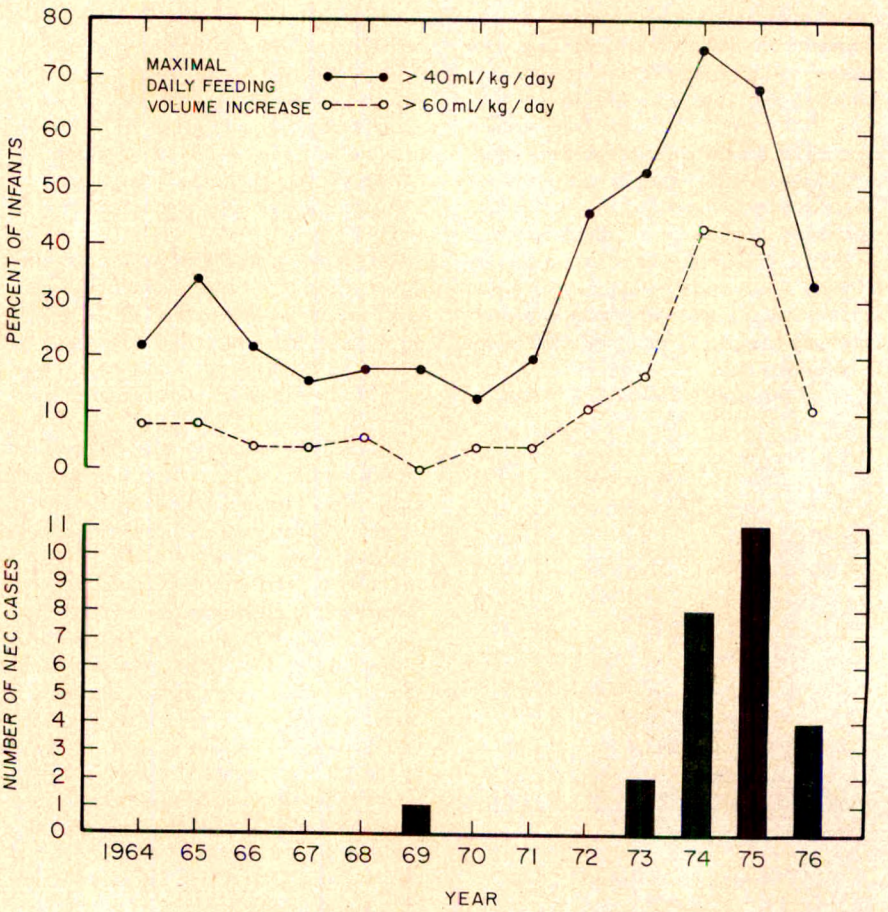

Fig 2.—Percentage of infants with rapid increase in feeding volume.

occurred ($P < .005$). Also, in 13 of the 15 infants who were subjected to one or more large daily feeding volume increases preceding NEC, a large daily increase occurred during the two days prior to the onset of NEC, and in 11 infants, on the day prior to the onset of NEC.

The 26 patients with NEC can be characterized as follows: (1) Thirteen had received large daily feeding volume increases within two days of the onset of NEC. These were large infants (nine > 1,500 g), with early onset of NEC (three to eight days for 11 infants). (2) Seven others were receiving large volumes (> 150 mL/kg/day) prior to the onset of NEC. These were small infants (six < 1,500 g), and all had NEC after seven days. (3) Four infants had had an exchange transfusion within two days of the onset of NEC. This group includes the infant who was never fed. (4) One infant had received a daily feeding volume increase of 55 mL/kg prior to the onset of NEC. (5) The 26th infant had not received a large daily feeding volume increase, a large daily feeding volume, or an exchange transfusion.

Of the 26 cases of NEC, 11 infants (43%) weighed less than 1,500 g at birth. Seventeen (65%) were male. The disease began at 3 to 7 days of age in 15 (54%) and at 8 to 35 days in the remainder. Oxygen therapy had been used for 21 infants (81%), and a respirator for nine (35%). Umbilical artery catheterization had been carried out in 18 babies (69%), and an exchange transfusion in six (23%). Fifteen infants had surgery, and ten of these died; nine of the 11 who were treated medically died. The overall mortality was 73%.

Seven different formulas had been used during this period. Thirteen infants received either Similac 20 or 24 (Ross Laboratories) or Enfamil 20

or 24 (Mead Johnson & Co); nine were given PM 60/40 (Ross Laboratories); three received hyperosmolar feeds (two, Nutramigen [Mead Johnson & Co] and one, Similac 27); and one infant was never fed. Intermittent gavage was used for 21 infants, continuous nasojejunal feedings for three and nipple feedings for one. Gluconate calcium was added to the diet of four infants.

COMMENT

With rare exception, NEC occurs after oral feedings have been given (63 of 64 cases[1]; 54 of 54[2]; 61 of 61[3]; 42 of 43[4]; 21 of 24[5]). In the present study, 25 of 26 infants were being fed at the onset of NEC.

In 1974, Krouskop et al[5] related NEC to overaggressive feeding. They reported that 18 of 24 infants with NEC had symptoms on an average of 31 hours after starting oral feedings (mean formula intake, 72 mL/kg/day). Brown and Sweet[6] later introduced a regimen of slowly progressive feeding to the New York Mount Sinai Hospital Neonatal Unit and then noted a dramatic drop in incidence of NEC, from 14 cases in 3½ years to one case in the subsequent four years.

Book et al[7] described a sharp increase in the incidence of NEC (from 0.3% to 5.1%) concurrent with the introduction of a more rapid increase of feeding volume. A total of 29 babies of birth weight less than 1,200 g were then randomly fed the mean feeding volume of either the "gradual-increase-of-feeding-volume" period or the "rapid-increase-of-feeding-volume" period. Necrotizing enterocolitis developed in three of 15 from the rapid-fed group and in two of 14 from the gradual-fed group, a statistically nonsignificant difference. These results are not persuasive for two reasons: (1) Use of a small sample size may have led to missing important differences.[8] (2) Use of the mean feeding rates in the randomized trial did not replicate the conditions in the naturally occurring gradual- and rapid-feeding periods. The fastest feeding rates at the top of the range of the rapid-feeding period (perhaps the most likely to produce NEC) were eliminated. Conformity to the mean in the gradual-feeding group did not allow for individual variation based on the infant's condition and response to feedings, which might have made NEC less likely in the gradual-feeding period.

Frantz et al[2] carried out a retrospective, case-control study of 54 cases of NEC and 98 weight-matched controls. All 54 cases of NEC were receiving oral feedings prior to the onset of NEC while *only 63% of controls were receiving oral feedings on the same day of life that symptoms developed in the matched NEC patient* ($P < .001$). The infants with NEC had more umbilical and arterial catheters, but they were equally ill as judged by Apgar scores, blood pressures, temperatures, presence of respiratory distress syndrome, and use of respirators. These data are strongly supportive of the hypothesis that feeding practices are of major etiologic importance in NEC.

Historical Perspective

Hess and Lundeen,[9] pioneers in the care of premature infants in the United States, wrote:

> The tendency to overfeed the young premature infant is undoubtedly one of the important factors in the mortality and morbidity found among premature babies during their first 3-6 weeks of life.

They recommended, "feeding very small amounts of food and then increasing the amount very slowly," and they advised not giving more than 100 cal/kg/day until the infant is at least a month old and then described vomiting and abdominal distention as possible consequences of overfeeding. It is worth noting that Hess and Lundeen's[9] recommendations define almost precisely the feeding boundary beyond which most of the infants of the present study had NEC, ie, increasing feeding volumes rapidly or giving more than 100 cal/kg/day (150 mL/kg/day of a 0.66 cal/mL formula) to an infant of birth weight less than 1,500 g within the first month of life (latest day of onset of NEC in our patients was 35 days).

Possible Mechanisms

Hasselmeyer and Hon[10] noted severe bradycardia in healthy premature infants receiving 10 to 45 mL of formula by gavage. In other studies, a marked decrease in Pao_2 levels was observed after feeding 4.7 to 8.0 mL/kg of either human milk or 5% dextrose water by gavage to premature and full-term infants with respiratory distress.[11,12] Gut ischemia has been considered a prime requisite for production of NEC.[6] The bowel that is compromised by perinatal asphyxia, respiratory distress syndrome, and exchange transfusions, which are recognized causes of gut ischemia and also recognized associations of NEC,[6] may then be subject to additional insult by the bradycardia and hypoxia that may result from feeding.

Tejani et al[13] observed a decrease in the blood pH and an increase in the blood lactate level shortly after ingestion of 1.75 g/kg of dextrose by formerly hypoxic premature and term infants. The authors attribute the lactic acidosis to hypoxic injury of the mechanism for glucose transport, resulting in malabsorbed intraluminal carbohydrate, which is then converted into organic acids. They hypothesize that malabsorbed carbohydrate may, by bacterial action, be the source of the gas of NEC pneumatosis.

References

1. Santulli TV, Schullinger JN, Heird WC, et al: Acute necrotizing enterocolitis in infancy: A review of 64 cases. *Pediatrics* 55:376-385, 1975.
2. Frantz ID, L'Heureux P, Engel RR, et al: Necrotizing enterocolitis. *J Pediatr* 86:259-263, 1975.
3. Roty AR, Kilway JB, Brown AL: Acute necrotizing enterocolitis in neonates. *Am Surg* 43:392-394, 1977.
4. Bell RS, Graham CB, Stevenson JK: Roentgenologic and clinical manifestations of neonatal necrotizing enterocolitis. *Am J Roentgenol Rad Ther Nucl Med* 112:123-127, 1971.
5. Krouskop RW, Brown EG, Sweet AY: The relationship of feeding to necrotizing enterocolitis, abstracted. *Pediatr Res* 8:383, 1974.
6. Brown EG, Sweet AY: Prevention of necrotizing enterocolitis. *JAMA* 240:2452-2454, 1978.
7. Book LS, Herbst JJ, Jung AL: Comparison of fast- and slow-feeding rate schedules to the development of necrotizing enterocolitis. *J Pediatr* 89:463-466, 1976.
8. Frieman JA, Chalmers TC, Smith H, et al: The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 299:690-694, 1978.
9. Hess JH, Lundeen EC: *The Premature Infant, Medical and Nursing Care*. Philadelphia, JB Lippincott Co, 1949, pp 115-116, 258-259.
10. Hasselmeyer EG, Hon EH: Cardio-respiratory changes associated with gavage feeding, abstracted. *Pediatr Res* 4:472, 1970.
11. Klein M, Harrison VC, Heese H deV: Impaired arterial oxygenation after feeding in newborn infants, abstracted. *Pediatr Res* 7:398, 1973.
12. Wilkinson A, Yu VYH: Immediate effects of feeding on blood-gases and some cardiorespiratory functions in ill newborn infants. *Lancet* 1:1083-1085, 1974.
13. Tejani N, Lifshitz F, Harper RG: The response to an oral glucose load during convalescence from hypoxia in newborn infants. *J Pediatr* 94:792-796, 1979.

Cardiac Function in Primary Hypothyroidism

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• Cardiac chamber dimensions and myocardial function were studied in 15 children with primary hypothyroidism prior to and after thyroxine therapy. Small pericardial effusions were detected in 11 of 15 subjects before therapy, which resolved in nine of 11 subjects after initiation of thyroxine replacement. There was no association between the severity of the thyroid failure and the presence of effusion, and no evidence of cardiac compromise due to effusions. No significant abnormality in cardiac chamber or myocardial dimensions, systolic time intervals, or indices of myocardial contractility was detected among the hypothyroid children as compared with a normal population. Neither myocardial dimensions nor contractility indices changed significantly on reestablishment of normal thyroxine concentrations with exogenous hormone. These data refute the existence of a myocardiopathy associated with hypothyroidism in children.

(*Am J Dis Child* 134:556-559, 1980)

The effect of hypothyroidism on cardiac function in children is, to our knowledge, incompletely characterized. Significant abnormalities in left ventricular function have been documented among hypothyroid adults. These observations dictated cautious institution of exogenous thyroid hormone in myxedematous adults to avoid myocardial decompensation. Whether a compromise of myocardial function exists among hypothyroid children is not well documented. To evaluate this possibility, myocardial chamber and muscle dimensions, systolic time intervals, and indices of ventricular performance were studied echocardiographically in a group of children with primary hypothyroidism prior to and after thyroxine therapy.

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SUBJECTS AND METHODS

Fifteen subjects, 13 females and two males, first observed at the pediatric endocrine clinic with historical, clinical, and laboratory evidence of primary hypothyroidism had echocardiographic evaluation of myocardial dimensions and function prior to (Table 1) and after (Table 2) initiation of L-thyroxine replacement therapy. The study population was heterogeneous with respect to the cause of the hypothyroidism, four of 15 having a diagnosis of congenital hypothyroidism and the remainder having acquired hypothyroidism, primarily due to chronic lymphocytic thyroiditis. Subject 11 was unique in that her hypothyroidism was secondary to thyroidectomy for papillary follicular carcinoma. Other than for this subject, the duration of the hypothyroidism was not easily documented. The initial echocardiograms were obtained at the time of diagnosis prior to the initiation of replacement hormone. Repeated echocardiograms were obtained at follow-up examination, at which time all subjects were receiving full-replacement thyroxine doses.

Echocardiograms were performed using an echocardiograph with a 3.5-mHz transducer. Tracings were recorded on a strip chart at a constant paper speed of 100 mm/s. Left ventricular diastolic dimension and left ventricular systolic dimension were measured in the standard manner.[1] Systolic time intervals were measured from the echocardiographic aortic value tracings. The preejection period (PEP) was measured from the Q wave of the standard lead II of the ECG to the first rapid opening deflection of the valve leaflets. The left ventricular ejection time (LVET) was recorded as the interval from opening to closing of the aortic valve leaflets.[2] The measured PEP, LVET, and calculated ratio PEP/LVET were compared with the expected normal values for age.[3] Percentage change in left ventricular dimensions and velocity of circumferential fiber shortening were calculated using the echocardiographic LVET according to the method of Gutgesell et al.[3] Heart rate was calculated from the R-R interval of the ECG. Serum thyroxine (T_4) and thyroid-stimulating hormone (TSH) were measured by radioimmunoassay in the hospital clinical laboratory, normal ranges being 4.5 to 12.5 μg/dL for T_4 and 0 to 10 μU/mL for TSH.

Statistical analysis of data using paired *t* tests, analysis of variance, and linear correlation was done by routine procedures available within a computerized statistical package[4] or on a programmable statistical calculator. Unless otherwise noted, summary data are expressed as mean and SEM.

RESULTS

All 15 subjects were hypothyroid at the time of diagnosis, mean serum T_4 concentration being 1.0 ± 0.2 μg/dL (range, < 0.1 to 2.5 μg/dL). Thyroid-stimulating hormone concentration was noticeably elevated in all subjects, the mean serum TSH concentration being 533 ± 81.6 μU/mL. At follow-up examination, all subjects showed clinical signs of resolution of their hypothyroidism. No subject had clinical or chemical evidence of hyperthyroidism induced by their replacement thyroxine. Although the serum T_4 concentrations were within the normal range for all subjects at their follow-up examination (mean $T_4 = 10.3 \pm 1.6$ μg/dL), the TSH concentration was incompletely suppressed by thyroxine replacement in six of 15 subjects (Table 2). Three of these subjects were less than 1 year of age and had relatively brief intervals between initiation of thyroxine replacement and follow-up study. Guyda et al[5] have previously noted the sluggish TSH response of congenitally hypothyroid infants during thyroxine replacement. In the older patients with incomplete TSH suppression, two of three had only modest elevations of TSH.

Table 1.—Myocardial Function Before Thyroxine*

Subject/ Age, yr	T_4, μg/dL	TSH, μU/mL	Effusion	Heart Rate, Beats/min	PEP, s	LVET, s	PEP/LVET	% Change in Left Ventricular Dimension During Systole	Velocity of Circumferential Fiber Shortening
1/.08	0.1	510	P	58	0.05	0.21	0.24	43	2.05
2/.33	2.5	800	A	136	0.05	0.18	0.28	34	1.89
3/.58	0.1	535	A	111	NA	NA	NA	20	NA
4/1.0	0.5	125	P	76	0.05	0.12	0.36	47	3.92
5/6.7	0.5	215	P	83	0.10	0.28	0.34	36	1.29
6/7.1	0.1	...	P	64	0.12	0.27	0.43	36	1.33
7/9.4	0.7	333	P	72	0.10	0.28	0.35	38	1.36
8/10.2	0.1	850	P	84	0.07	0.23	0.24	42	1.34
9/12.8	2.2	800	A	73	NA	0.20	NA	39	1.95
10/13.1	0.3	999	P	71	0.09	0.28	0.32	38	1.36
11/13.8	0.8	96	A	63	0.09	0.31	0.30	32	1.03
12/13.9	2.3	340	P	51	NA	NA	NA	48	NA
13/15.3	2.2	...	P	71	0.14	0.29	0.50	31	1.07
14/15.6	2.2	600	P	73	0.11	0.28	0.39	34	1.36
15/16.0	1.0	730	P	63	NA	NA	NA	31	NA

*PEP indicates preejection period; LVET, left ventricular ejection time; T_4, serum thyroxine; TSH, thyroid-stimulating hormone; P, effusion present; A, effusion absent, and NA, not available, echocardiographic tracing inadequate.

Table 2.—Myocardial Function After Thyroxine*

Subject/ Age, yr	T_4, μg/dL	TSH, μU/mL	Effusion	Heart Rate, Beats/min	PEP, s	LVET, s	PEP/LVET	% Change in Left Ventricular Dimension During Systole	Velocity of Circumferential Fiber Shortening
1/.17	12.0	44	A	150	0.05	0.20	0.22	41	2.05
2/.75	8.0	33	A	150	NA	0.21	NA	55	2.65
3/.58	7.0	285	A	142	0.05	0.17	0.31	23	1.35
4/1.1	11.3	16	A	110	0.07	0.16	0.39	38	2.38
5/6.8	12.5	5	A	84	0.10	0.30	0.33	38	NA
6/7.3	9.2	2	A	96	0.09	0.31	0.30	32	1.03
7/9.7	8.6	1	A	80	0.06	0.29	0.21	42	1.45
8/10.5	8.7	51	P	74	0.09	0.26	0.33	35	1.19
9/13.8	8.1	13	A	68	0.10	0.27	0.33	38	1.44
10/13.8	12.1	6	A	73	NA	0.28	NA	45	1.61
11/13.6	9.4	5	A	81	0.08	0.28	0.32	39	1.39
12/14.1	11.3	3	A	90	NA	NA	NA	44	NA
13/15.7	12.6	3	A	70	NA	0.31	NA	37	1.19
14/15.8	10.0	2	P	84	0.07	0.28	0.25	32	1.14
15/16.2	10.5	4	A	78	0.06	0.29	0.20	40	1.38

*T_4 indicates serum thyroxine; TSH, thyroid-stimulating hormone; A, effusion absent; P, effusion present; PEP, preejection period; LVET, left ventricular ejection time; and NA, not available—echocardiographic tracing inadequate.

Small pericardial effusions were detectable in 11 of the 15 subjects at the time of diagnosis. The presence of pericardial effusions did not seem to compromise cardiac function in that there was no statistical difference in clinical and echocardiographic indices of myocardial function between subjects with effusions compared with those without effusions. At follow-up examination, the pericardial effusions had resolved in nine of 11 subjects. The two subjects with persisent effusions were not different with respect to initial or follow-up thyroid function tests or with respect to duration of therapy from those subjects in whom effusions resolved.

There was a significant increase in heart rate after initiating replacement with thyroxine ($P < .01$); however, no significant differences in systolic, diastolic, or mean blood pressure were detectable. Cardiac chamber and ventricular wall dimensions were within the normal limits for age prior to thyroxine replacement. No systematic deviation of these measurements from normal were noted. Furthermore, no significant change in these dimensions compared with pretreatment measurements was detected after the reestablishment of the serum thyroxine concentrations within the normal range.

Systolic time intervals among hypothyroid subjects were not statistically different from those observed among euthyroid control populations. The PEP among hypothyroid individuals was less than expected for heart rate in two of the ten subjects (Fig 1), the remainder having PEPs within or greater than expected. Left ventricular ejection time among hypothyroid subjects (Fig 2) showed less deviation from the expected, with three of the 12 subjects falling outside the normal range. Neither the PEP nor the LVET showed a systematic trend in the direction of deviation from normal sub-

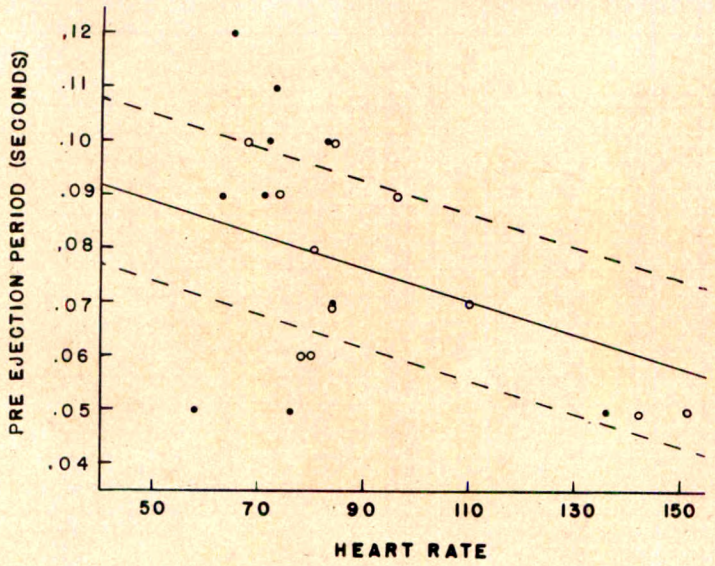

Fig 1.—Preejection period of subjects prior to (closed symbols) and after (open symbols) thyroxine replacement, superimposed on heart rate (beats/min) scaled normative data (mean ± 2 SD) (from Gutgesell et al[3]).

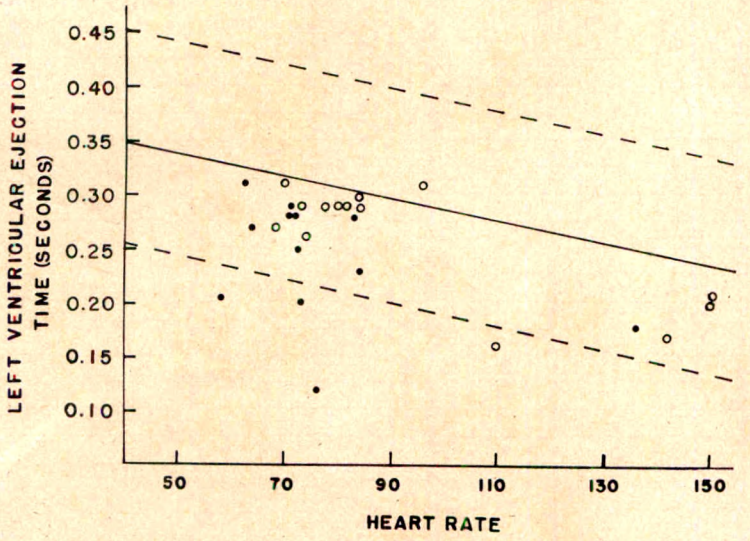

Fig 2.—Left ventricular ejection time of subjects prior to (closed symbols) and after (open symbols) thyroxine replacement, superimposed on heart rate (beats/min) scaled normative data (mean ± 2 SD) (from Gutgesell et al[3]).

jects either prior to or after reestablishment of normal serum thyroxine concentrations. There was no statistically significant correlation between subjects' systolic time intervals or the degree of deviation of the systolic time intervals from normal and the variables of thyroid function. The PEP/LVET ratios were not significantly different than normal. There was a wide scatter in the ratios among hypothyroid subjects, thus reflecting the augmented error inherent in ratios of inversely related variables.

Myocardial contractility, as expressed by the percent of change in left ventricular diameter, was not statistically different from that in a normal population (Fig 3). Three of the 15 determinations among hypothyroid individuals were outside the normal range; however, there was no systematic trend in the direction of this change from normal. Data for velocity of circumferential fiber shortening also showed no significant ($P > .05$) change from normal, although there was wide scatter in the observed compared with expected values. As with the systolic time intervals, there was no significant correlation between the percent change in left ventricular diameter or velocity of circumferential fiber shortening and indices of thyroid function.

COMMENT

Our observations of echocardiographically determined myocardial dimensions and indices of myocardial function show no significant deviation of these values from normal among hypothyroid children. Among the values measured, only heart rate showed a significant ($P < .05$) change on re-

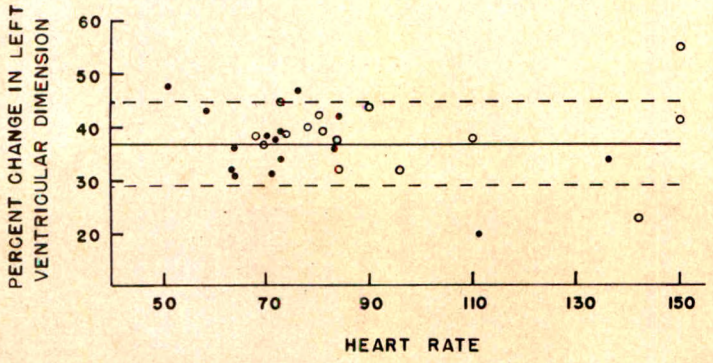

Fig 3.—Percent of change in left ventricular dimension of subjects prior to (closed symbols) and after (open symbols) thyroxine replacement, superimposed on heart rate (beats/min) scaled normative data (mean ± 2 SD) (from Gutgesell et al[3]).

establishment of normal serum T_4 concentrations with exogenous hormone. Although six of the 15 subjects were not euthyroid by the criteria of normalization of TSH concentration at the time of follow-up study, there was no systematic trend in the direction of change of their indices of cardiac function compared with the other nine subjects. This limitation in the data, therefore, should not skew the analysis. The change in heart rate is probably both a direct action of thyroid hormone on the myocardium as well as an indirect effect necessitated by reestablishment of a normal metabolic rate and, therefore, increased peripheral tissue oxygen requirements.[6]

Our observations in hypothyroid children are in contrast to the reported abnormalities in systolic time intervals among hypothyroid adults.[7,8] The reports on adult subjects documented prolonged PEP, shortened LVET, and abnormal PEP/LVET ratios in hypothyroid adults. In addition, Hillis et al[8] documented a significant correlation between systolic time intervals and the degree of thyroid hormone deficiency. No significant correlation was noted in our population between any of the indices of myocardial function and thyroid function tests.

There are limited data on myocardial contractility among hypothyroid adults. Graettinger et al[6] found that severely hypothyroid adults had normal cardiac reserve to exercise stress testing. Our data indicate that hypothyroid children have no alternation in myocardial contractility as measured by the percentage of change in left ventricular dimensions or the velocity of circumferential fiber shortening.

The frequency of pericardial effusions accompanying hypothyroidism appears greater in children than adults. Kerber and Sherman[9] reported that 30% of their 33 adult subjects had echocardiographically detectable pericardial effusions compared with the 73% frequency observed in our younger population. The reason for the discrepancy is unknown; however, the duration of hypothyroidism and age at diagnosis may be important variables. Despite the frequent occurrence of effusions among our hypothyroid subjects, the presence of effusions was not associated with clinically detectable cardiac dysfunction nor with abnormality in echocardiographic indices of cardiac function. Although enlargement of the cardiac silhouette in hypothyroidism is common,[6,9,10] our data suggest that this does not reflect dilated cardiac chambers due to a myxedematous myocardium. Rather, the "cardiomegaly" of hypothyroidism in children is more likely the result of a pericardial effusion in the presence of normal cardiac contractility and chamber size.

Rapid but cautious reestablishment of normal serum T_4 concentrations among hypothyroid subjects is the goal of replacement hormone therapy. Although significant alternations in cardiac function among hypothyroid adults have been reported, our echocardiographic evaluation detected neither any systematic alternation in cardiac chamber or myocardial dimensions nor any decrease in myocardial function among profoundly hypothyroid children. This difference between adults and children may reflect the presence of additional complicating myocardial disease, such as atherosclerotic coronary artery disease, coexisting in the hypothyroid adult population. Our observations in children indicate that myocardial function does not seem to be a limiting factor in determining the rapidity of L-thyroxine replacement therapy.

References

1. Sahn DJ, DeMaria A, Kisslo J, et al: Recommendation regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 58:1072-1083, 1978.

2. Hirschfeld S: Measurement of right and left ventricular systolic time intervals by echocardiography. *Circulation* 51:304-309, 1975.

3. Gutgesell HP, Paquet M, Duff DF, et al: Evaluation of left ventricular size and function by echocardiography. *Circulation* 56:457-462, 1977.

4. Barr AJ, Goodnight JH, Sall JP, et al: *A User's Guide to SAS76*. Raleigh, NC, Sparks Press, 1976.

5. Guyda H, Letarte J, Dussault J, et al: Serum levels of T_4, T_3 and TSH during therapy of neonatal hypothyroidism. *Pediatr Res* 11:426, 1977.

6. Graettinger JS, Muenster JJ, Checchia CS, et al: A correlation of clinical hemodynamic studies in patients with hypothyroidism. *J Clin Invest* 37:502-510, 1958.

7. Bough WE, Crowley WF, Ridgeway EC, et al: Myocardial function in hypothyroidism. *Arch Intern Med* 138:1476-1480, 1978.

8. Hillis WS, Bremner WF, Lawrie TD, et al: Systolic time intervals in thyroid disease. *Clin Endocrinol* 4:617-624, 1975.

9. Kerber RE, Sherman B: Echocardiographic evaluation of pericardial effusion in myxedema. *Circulation* 52:823-827, 1975.

10. Contis G, Nadas AS, Crigler JF Jr: Cardiac manifestations of congenital hypothyroidism in infants. *Pediatrics* 38:452-456, 1966.

Cefaclor in Treatment of Otitis Media and Pharyngitis in Children

Samuel E. McLinn, MD

• **The safety and efficacy of cefaclor were compared with amoxicillin trihydrate in the treatment of 130 cases of otitis media, and with penicillin V potassium in 88 cases of streptococcal pharyngitis in two single-blind controlled studies. Patients with otitis media received approximately 40 mg/kg/day of cefaclor or amoxicillin trihydrate for ten days to three weeks; patients with pharyngitis received 20 mg/kg/day of cefaclor or penicillin V potassium for ten days. Overall, patients who received cefaclor for otitis media had fewer acute failures and better total success, especially in cases caused by *Haemophilus influenzae*; however, the difference between cefaclor and amoxicillin was not statistically significant. There also was no significant difference between the clinical effectiveness of cefaclor and penicillin in the treatment of streptococcal pharyngitis. Cefaclor was well tolerated with no serious side effects.**

(*Am J Dis Child* 134:560-563, 1980)

Otitis media and streptococcal pharyngitis, with their high incidence and disturbing relapse rates, are two of the most prevalent infections of childhood. Bluestone has termed otitis media with effusion "the most common diagnosis made by physicians who provide care for children (second only to the common cold)."[1] Studies from various populations have shown that 76% to 95% of all children have at least one episode of otitis media by the age of 6 years.[2,3] Of infants in whom middle ear infections develop at less than 1 year of age, about one half become otitis prone.[4] Permanent structural changes have been reported in as many as 32% of these chronically infected children. Recent literature has shown more insidious complications, such as learning disabilities, lowering of intelligence, and social and language difficulties as a result of impaired hearing.[5-8]

Antibiotics, principally penicillin and penicillin analogs like ampicillin, have contributed to the reduction of such problems. However, there seems to be an increasing number of reports of the development of ampicillin-resistant strains of *Haemophilus influenzae*, both typable and nontypable, which are a major cause of otitis media in young children.[9-14]

Streptococcal pharyngitis also represents a most common and often persistent bacterial infection in children. The selection of the appropriate antibiotic and compliance with the recommended ten-day dosage regimen may be prophylactic as well as therapeutic, possibly preventing both rheumatic fever (an almost extinct entity in this part of the world today) and acute glomerulonephritis. However, it has been estimated that streptococci persist in the pharynx in 10% to 25% of the children who complete a ten-day regimen of penicillin for acute pharyngitis.[15,16] The high persistence and recurrence rates have been attributed to one or more of such factors as failure of the patient to complete the full course of treatment, inactivation of penicillin by β-lactamase-producing staphylococci present in the upper respiratory tract, a high rate of homologous streptococci in household contacts, and the M and T typability of pathogenic isolates.

Cefaclor is a new oral cephalosporin antibiotic with in vitro activity against *Streptococcus pneumoniae*, *H influenzae*, β-hemolytic streptococci, and *Staphylococcus aureus*, organisms commonly found in upper respiratory tract infections of infants and children. This spectrum of activity sug-

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Table 1.—Results of Treatment—218 Patients*

Diagnosis/ Treatment	N	Cure (%)	Failure (%)	Reinfection or Relapse (%)
Otitis media				
Cefaclor	64	59 (92)	3 (5)	2 (3)
Amoxicillin	66	58 (88)	6 (9)	2 (3)
Pharyngitis				
Cefaclor	43	38 (88)	3 (7)	2 (5)
Penicillin VK	45	39 (87)	3 (7)	3 (7)

*Cure indicates disappearance or improvement of signs and symptoms during therapy and elimination of pathogen or reduction of pathogen(s) to insignificant numbers; reinfection, initial elimination of pathogen followed by infection with new organism during ten- to 21-day follow-up period; relapse, initial elimination of pathogen followed by recurrence of same organism during ten- to 21-day follow-up period; and failure, no improvement of signs and symptoms of infection and persistence of pathogen on culture.

Table 2.—Distribution of Organisms in 130 Cases of Otitis Media

Organism	N (%)
Streptococcus pneumoniae	74 (54)
Haemophilus influenzae	34 (25)
Streptococcus, group A	11 (8)
Staphylococcus aureus	10 (7)
Neisseria catarrhalis	8 (6)
Total	**137 (100)**

Table 3.—Results by Organism—137 Isolates in 130 Patients With Otitis Media

	Cefaclor, Cure/Total (%)	Amoxicillin Trihydrate, Cure/Total (%)
Streptococcus pneumoniae	36/37 (97)	33/37 (89)
Haemophilus influenzae	17/20 (85)	11/14 (79)
Streptococcus, group A	5/6 (83)	4/5 (80)
Staphylococcus aureus	3/3 (100)	7/7 (100)
Neisseria catarrhalis	2/2 (100)	6/6 (100)
Total	**63/68** (93)	**61/69** (88)

gests that cefaclor would be an acceptable alternative treatment for otitis media and streptococcal pharyngitis in pediatric patients.

This is a report of two studies: comparison of the safety and efficacy of cefaclor and amoxicillin trihydrate in the treatment of otitis media, and of cefaclor and penicillin V potassium in the treatment of streptococcal pharyngitis.

MATERIALS AND METHODS

A total of 218 infants and children with acute otitis media (130) or streptococcal pharyngitis (88) were treated as private outpatients in two single-blind controlled studies. Assignment to the drug groups was made according to a computerized random distribution table. Informed consent was obtained from a parent in all cases.

The paired groups were comparable with regard to age and distribution of ages. The otitis media patients ranged from 1 month to 11 years of age, with a mean age of 2.7 years for the cefaclor group and 2.6 years for the amoxicillin group. Twenty-eight (44%) of the 64 patients who received cefaclor and 31 (47%) of the 66 patients who received amoxicillin were younger than 2 years of age. In the patients with pharyngitis, ages ranged from 1 to 17 years, with mean ages of 7.5 years for the cefaclor group and 7.1 years for the penicillin group.

Patients with otitis media received approximately 40 mg/kg/day of cefaclor or amoxicillin trihydrate for ten days to three weeks (mean, 12.4 days) depending on the clinical and bacteriologic response, and patients with pharyngitis received 20 mg/kg/day of cefaclor or penicillin V potassium for ten days. The maximum daily dose of all three antibiotics was 750 mg.

Compliance with the dosage regimen was monitored by requiring the parent to bring the medication bottle to the office visits; the bottle was weighed and compliance was determined by the weight and volume differential.

Bacteriologic methods for patients with otitis media included cultures of ear exudate (obtained by Senturia aspirator[17]) at the beginning of therapy and again 48 hours later. Clinical evaluation was made at the end of therapy and ten to 21 days later.

Throat cultures were obtained from patients with pharyngitis at the start of treatment, and the presence of group A streptococcus was determined by bacitracin disks, 0.04 units (Taxos A disks). Quantitative estimation of 40 colonies or more was required. Follow-up cultures were taken at 12 to 14 days and again two to three weeks after the end of treatment. Specimens were assayed for M and T typing at the Center for Disease Control, Atlanta. All organisms were tested for susceptibility by the Food and Drug Administration Standardized Disk Method.

Evaluation of safety was based on close observation of clinical and laboratory effects. Monitoring included pretherapy and end-of-therapy tests for complete blood cell count, platelet estimation, Coombs' test, BUN, serum creatinine, SGOT and/or SGPT, bilirubin, alkaline phosphatase levels, and urinalysis (including microscopic examination).

RESULTS

Otitis Media

The overall results are given in Table 1. The clinical and bacteriologic success rate for cefaclor was 92% (59 cures in 64 patients) and for amoxicillin 88% (58 cures in 66 patients). The terms of response as used in this study (cure, failure, reinfection, and relapse) are defined in Table 1.

Three cases (5%) failed to respond to cefaclor; the causative organism in two of these failures was *H influenzae* and in the other was *Strep pneumoniae*. Amoxicillin failed to eliminate the causative organisms in six cases (9%); two were *Strep pneumoniae* alone, two were *H influenzae* alone, one was a mixed *Strep pneumoniae* and *H influenzae* infection, and one was β-hemolytic group A streptococcus.

In each group, two patients had initial cures followed by recurrences during the follow-up period ten to 21 days after the end of therapy (Table 1). In the two cases treated with cefaclor, the recurrent organism was different from the original pathogen; these, therefore, could be considered "reinfections" rather than acute "relapses." Two patients who received amoxicillin had a relapse of the original pathogen during the follow-up period.

Although patients who received cefaclor had fewer acute failures and better total success than patients who

received amoxicillin, the difference between the two antibiotics was not statistically significant.

As given in Table 2, of 137 isolates found in the 130 patients, *Strep pneumoniae* was the most frequent—74 isolates or 54%. *Haemophilus influenzae* (nontypable) occurred in 25% (34 of 137 isolates). Eight percent of the organisms were β-hemolytic group A streptococcus, 7% were *Staph aureus*, and 6% were *Neisseria catarrhalis*.

Four patients in the cefaclor group and three in the amoxicillin group had infections due to multiple organisms. All responded satisfactorily except one who received amoxicillin whose otitis media was caused by a combination of *Strep pneumoniae* and *H influenzae*.

Cefaclor seemed superior to amoxicillin against both *Strep pneumoniae* and *H influenzae* (Table 3). For example, 97% of the isolates of pneumococci (36 of 37) were eliminated by cefaclor compared with 89% (33 of 37) by amoxicillin. Against *H influenzae*, the success rates were 85% (17 of 20) and 79% (11 of 14) for cefaclor and amoxicillin, respectively.

Streptococcal Pharyngitis

There was no difference between the clinical effectiveness of cefaclor and penicillin in the treatment of 88 patients with streptococcal pharyngitis (Table 1). Success rates were 88% and 87%, respectively. Acute failures occurred in three patients of each group. Follow-up throat cultures at 14 to 21 days revealed two relapses attributed to cefaclor and three attributed to amoxicillin.

Four serologic types of group A streptococci were identified by M and T agglutination tests of the strains isolated from cases that were either bacteriologic recurrences or failures. Types 1, 4, 12, and 28 were found, with type 12 accounting for about one half the failures/recurrences. All relapses within the 21 days of the study period were homologous. In two additional cases, treated with cefaclor, recurrence of infection occurred 36 and 45 days, respectively, after the end of treatment, with serologic types different from the original strains. Both were type 12 initially but reappeared as type 2 in one case and as type 28 in the other. Because of the length of time between initial cure and reinfection and the appearance of new serologic types, these two cases were classified as "cures."

Adverse Reactions

Cefaclor demonstrated a low incidence of adverse clinical reactions and abnormal laboratory values. No gastrointestinal symptoms were reported in the 107 children who received cefaclor in these studies nor in the 45 patients who received penicillin. In the 66 patients who received amoxicillin, there was one report of diarrhea attributed to the drug therapy but treatment was not discontinued. Six other children had diarrhea, one had vomiting, and one complained of abdominal pain, but a direct association with amoxicillin was not established.

One case of vascular purpura occurred on the sixth day of treatment in a 5-year-old boy with otitis media due to *Strep pneumoniae* who received 250 mg of cefaclor three times daily. Although there was no history of allergy, cefaclor therapy was discontinued as a precautionary measure; there were no hematologic changes. The patient had responded well and further treatment was not indicated. No petechiae were present at the three-week follow-up visit.

COMMENT

Although *Strep pneumoniae* and *H influenzae* are considered the major targets in the treatment of otitis media in children, group A β-hemolytic streptococcus has been reported to cause from 2% to 8% of the cases[1,18-20] and cannot be considered an unimportant pathogen. One alternative therapeutic agent, trimethoprim-sulfamethoxazole, like cefaclor, has been found effective against both ampicillin-susceptible and ampicillin-resistant *H influenzae*. However, unlike cefaclor, it is not recommended for group A streptococcus.

Just as we must be aware of group A streptococcus as an important cause of otitis media, *Staph aureus* is another easily overlooked potential pathogen. Reports of its incidence range from 2% to 12% of the cases.[1,19] It is often resistant (penicillinase-producing) and the penicillins would not be effective.

Our patient population had approximately 8% of each of these Gram-positive organisms. Choice of an antibiotic that is not effective against both β-hemolytic streptococcus and *Staph aureus* could, theoretically, invite initial failure in 4% to 10% or more of patients. The spectrum of cefaclor includes both group A streptococcus and *Staph aureus* (both ampicillin-susceptible and ampicillin-resistant). Our results in a small number of patients with these pathogens (Table 3) suggest that cefaclor offers an acceptable alternative in the treatment of children with otitis media.

In this study, four children with *H influenzae* resistant to ampicillin but susceptible to cefaclor successfully received cefaclor, an encouraging finding in light of the ongoing problem of increased resistance of *H influenzae* to the penicillin analogs. Although the overall results did not show a substantial difference between cefaclor and amoxicillin in the treatment of otitis media, cefaclor did seem to be slightly better than amoxicillin in the cases caused by *H influenzae*.

It was shown in an earlier report[21] that cefaclor achieved measurable concentrations (0.01 to 7 μg/mL) in the exudate of the middle ear, as did amoxicillin and ampicillin (both 0.01 to 3 μg/mL).

Although all our cases of *H influenzae* otitis media were children and infants 5 years of age or younger, there is evidence that this organism is a more frequent pathogen in the older (school-age) child than formerly thought.[22] This underscores the importance of choosing an antibiotic with proved effectiveness against *H influenzae* in the treatment of otitis media in children of all ages.

Penicillin remains the drug of choice in streptococcal pharyngitis. However, if failure does occur and retreatment is necessary to prevent suppurative complications or to eliminate persistent streptococci from the pharynx, cefaclor is an alternative.

Cefaclor may offer some advantage if, as has been suggested,[23,24] penicillinase-producing staphylococcus is a factor in the failure of penicillin to eradicate group A streptococcus from the pharynx. The cephalosporins have a better record against coagulase-positive staphylococci than do the penicillins.

An important practical factor in antibiotic therapy of children is their willingness to comply with the dosage regimen. In our child patients, the palatability of cefaclor preparations has been rated higher than that of the penicillins.

In these single-blind, randomized, controlled studies, cefaclor was found at least as effective as other often-used medications in treating two of the most common infections of childhood. Its effectiveness in treating otitis media caused by *H influenzae* is particularly notable, and it was well tolerated.

Nonproprietary Names and Trademarks of Drugs

Amoxicillin trihydrate—*Amoxil, Larotid, Robamox Robicaps, Sumox, Trimox.*
Cefaclor—*Cefaclor.*

References

1. Medical News: The changing picture of otitis media in childhood. *JAMA* 242:707-709, 1979.
2. Bluestone CD, Shurin PA: Middle ear disease in children: Pathogenesis, diagnosis, and management. *Pediatr Clin North Am* 21:379-400, 1974.
3. Howie VM: Natural history of otitis media. *Ann Otol Rhinol Laryngol* 84(suppl 19):67-77, 1975.
4. Howie VM, Ploussard JH, Sloyer J: The "otitis-prone" condition. *Am J Dis Child* 129:676-678, 1975.
5. English GM, Northern JL, Fria TJ: Chronic otitis media as a cause of sensorineural hearing loss. *Arch Otolaryngol* 98:18-22, 1973.
6. Holm VA, Kunze LH: Effect of chronic otitis media on language and speech development. *Pediatrics* 43:833-839, 1969.
7. Jordan RE: Secretory otitis media in etiology of cholesteatoma. *Arch Otolaryngol* 78:261-265, 1963.
8. Freeman BA, Parkins C: The prevalence of middle ear disease among learning impaired children: Does a higher prevalence indicate an association? *Clin Pediatr* 18:205-212, 1979.
9. Crossen FJ Jr, Watson WC III, Bailey DW, et al: Acute otitis media caused by ampicillin-resistant *Haemophilus influenzae* type b. *JAMA* 236:2778-2779, 1976.
10. Khan WN, Rodriguez WJ, Friedman GL, et al: Incidence of ampicillin-resistant strains of *Haemophilus* species in the Greater Washington area, abstracted. *Arch Dis Child* 51:400, 1976.
11. Granoff DM, Basden M, Rockwell R: Ampicillin-resistant *Haemophilus influenzae*: Emergence in California's central valley. *West J Med* 128:101-105, 1978.
12. Overturf GD, Wilkins J, Leedom JM, et al: Susceptibility of *Haemophilus influenzae*, type b, to ampicillin at Los Angeles County/University of Southern California Medical Center: A reappraisal after ten years. *J Pediatr* 87:297-300, 1975.
13. Syriopoulou V, Scheifele D, Smith AL, et al: Increasing incidence of ampicillin resistance in *Haemophilus influenzae*. *J Pediatr* 92:889-892, 1978.
14. Nelson JD: Should ampicillin be abandoned for treatment of *Haemophilus influenzae* disease? *JAMA* 229:322-324, 1974.
15. Rosenstein BJ, Markowitz M, Goldstein E, et al: Factors involved in treatment failures following oral penicillin therapy of streptococcal pharyngitis. *J Pediatr* 73:513-520, 1968.
16. Green JL, Ray SP, Charney E: Recurrence rate of streptococcal pharyngitis related to oral penicillin. *J Pediatr* 75:292-294, 1969.
17. Senturia BH, Gessert CF, Carr CD, et al: Studies concerned with tubotympanitis. *Ann Otol Rhinol Laryngol* 67:440-467, 1958.
18. Kamme C, Lundgren K, Mardh P-A: The aetiology of acute otitis media in children. *Scand J Infect Dis* 3:217-223, 1971.
19. Brook I, Finegold SM: Bacteriology of chronic otitis media. *JAMA* 241:487-488, 1979.
20. Sorensen H: Antibiotics in suppurative otitis media. *Otolaryngol Clin North Am* 10:45-50, 1977.
21. McLinn SE: Comparative study of cefaclor: A new cephalosporin, and amoxicillin in the treatment of acute otitis media in children, in Siegenthaler W, Luthy R (eds): *Current Chemotherapy.* Washington, DC, American Society for Microbiology, 1978, pp 123-125.
22. Schwartz R, Rodriguez WJ, Khan WN, et al: Acute purulent otitis media in children older than 5 years: Incidence of *Haemophilus* as a causative organism. *JAMA* 238:1032-1033, 1977.
23. Knudsin R, Miller J: Significance of the *Staphylococcus aureus* carrier state in the treatment of disease due to group A streptococci. *N Engl J Med* 271:1395-1397, 1964.
24. Frank P, Miller L: Antagonistic effect of a penicillinase-producing staphylococcus on penicillin therapy of a streptococcal throat infection. *Am J Med Sci* 243:582-585, 1962.

Chronic Otitis Media in Children

Microbiological Studies

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• **Aspiration of the exudate through the open perforation was performed in 68 children with chronic otitis media. The middle ear aspirate and a swab specimen of the external auditory canal were cultured aerobically and anaerobically. Seventy-eight isolates were recovered from the middle ears, 99 from the external ear canals, and 95 were present at both sites. Aerobes only were isolated from 33 patients (48.5%), nine (13.2%) had only anaerobes, and 26 (38%) had a culture that grew both aerobes and anaerobes. There were 99 aerobic isolates. Aerobes commonly recovered were *Pseudomonas aeruginosa, Staphylococcus aureus, Proteus* sp, *Klebsiella pneumoniae,* and *Haemophilus influenzae.* There were 74 anaerobes isolated. Anaerobes commonly isolated were anaerobic Gram-positive cocci, *Bacteroides* sp, and *Clostridium* sp. These findings demonstrate the polymicrobial bacteriology of chronic otitis media in children. Cultures collected from the external auditory canals prior to their sterilization can be misleading. Reliable information can be obtained from the ear exudates when collected through the open perforation in the tympanic membrane.**

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Chronic otitis media in children can be insidious, persistent, and very often destructive, with sometimes irreversible sequelae, such as hearing deficit and subsequent learning disabilities. The bacterial flora of chronic otitis media with perforation has not been studied systematically in pediatric patients with use of good anaerobic techniques, although a few older studies indicated that anaerobic bacteria played an important role in this condition.[1]

The present study was undertaken to determine the bacteriology of chronic otitis media with perforation in children. Modern anaerobic and aerobic methodologies were used in an attempt to compare the bacteria isolated from the external auditory canal with those isolated in the middle ear. This comparison is of particular importance, since in many instances clinicians collect the specimens from the external auditory canal, allowing contamination by skin flora.

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SUBJECTS AND METHODS

Patients

Middle ear exudate was aspirated from children suffering from chronic otitis media with perforation. Sixty-eight children were included in this study. The patients' ages ranged from 4 to 16 years (average, 11 years and 2 months). All suffered from mental retardation of varying severity. All were examined at the outpatient Ear, Nose, and Throat Clinic, Washington, DC, between June 1, 1976, and July 30, 1977, for their chronic otitis media. Patients had purulent drainage and a perforated tympanic membrane, and none had cholesteatoma. History of prior operative procedure was obtained in 16 patients. Five had tympanoplasty, and 11 had placement of ventilating tubes. However, none had tympanostomy tubes at the time of cultures, or three months previously. The duration of the chronic otitis media with perforation ranged from six months to eight years (average, three years and eight months). All patients had received previous courses of antimicrobial therapy for their infection. Eight had received one course, 15 had received two courses, and 45 had been treated three times or more. However, patients received no local or parenteral antimicrobial therapy for at least one month prior to sample collection.

Culture Technique

A culture of the external auditory canal was obtained using a swab soaked in sterile saline solution. The swab was immediately plated for aerobic and anaerobic bacteria. Thereafter, the external ear canal was cleaned of cerumen and pus with a blunt curette when indicated, and was swabbed with povidone-iodine (Betadine) and then with 70% alcohol solution, and allowed to dry for two to three minutes. A repeated culture of the external auditory canal was performed in a similar fashion, to document the sterility of the external canal. Collection of the exudate was done through the perforation in the tympanic membranes using a device consisting of an 18-gauge needle covered by a plastic cannula and attached to a 2-mL syringe. The needle was bent to a 45° angle, and the cannula was slipped forward to cover the tip. When the tympanic membrane was approached via an otoscope, the cannula was retracted and the eardrum was entered through the perforation and the exudate was collected. Thus, no contact was made by the needle tip with the speculum or the auditory canal, and no pus was collected from other than the middle ear.

Microbiological Methods

The aspirated fluid was diluted in 0.5 mL of thioglycolate broth and was immediately inoculated onto aerobic and anaerobic media. Sheep blood agar, chocolate agar, and MacConkey's agar plates were inoculated for aerobes. The plates were incubated at 37 °C aerobically (MacConkey's agar plates) or under 5% carbon dioxide and examined at 24 and 48 hours. For anaerobes, the material was plated on prereduced vitamin K_1-enriched *Brucella* blood agar, and anaerobic blood agar plate containing kanamycin sulfate and vancomycin hydrochloride, and placed into enriched thioglycolate broth (containing hemin, sodium bicarbonate, and vitamin K_1).[2] The brucella plates were incubated in anaerobic jars and examined at 48 and 96 hours. The thioglycolate broth was incubated for 14 days. Anaerobes were identified by techniques previously described.[2] Aerobic bacteria were identified using conventional methods.

Organisms recovered only from the external auditory canal were considered to be a contaminant. Bacteria present in both the auditory canal and the middle ear were listed separately and were added to the total number of middle ear isolates.

RESULTS

One hundred and eight middle ear aspirates were obtained from the 68 patients. In 40 patients, bilateral aspiration was performed, and in 19 of them identical bacteria were isolated from both middle ears. In the other 21 patients, differences were noted between the bacterial isolates of both middle ears; 14 differed in one isolate, four in two, and three in three or more isolates. The major bacteria accounting for these differences were *Pseudo-*

Table 1.—Aerobic and Facultative Isolates From External Canal and Middle Ear From 68 Patients With Chronic Otitis Media With Perforation

Aerobic and Facultative	External Canal and Middle Ear Isolates: Present in External Canal Only	External Canal and Middle Ear Isolates: Present in Middle Ear Only	External Canal and Middle Ear Isolates: Present in Both External Canal and Middle Ear	Middle Ear Isolates: Present in Mixed Culture	Middle Ear Isolates: Present in Pure Culture	Middle Ear Isolates: Total No. of Isolates	% of Patients
Gram-positive cocci							
Streptococcus pneumoniae	...	3	2	5	...	5	7
a-hemolytic streptococci	8	1	1	2	...	2	3
Group A, β-hemolytic streptococci	2	1	2	2	1	3	4
Staphylococcus aureus	3	7	8	11	4	15	22
Sta epidermidis	32	1	3	4	...	4	6
Gram-negative bacilli							
Haemophilus influenzae	...	4	2	6	...	6	9
Proteus mirabilis	3	2	5	5	2	7	10
P rettgeri	1	1	1	2	...	2	3
Proteus sp	5	...	1	1	...	1	1
Pseudomonas aeruginosa	16	14	19	27	6	33	48
Klebsiella pneumoniae	1	3	4	5	2	7	10
Escherichia coli	...	3	2	5	...	5	7
Serratia marcescens	2	...	2	2	...	2	3
Providencia sp	...	2	1	3	...	3	4
Citrobacter diversus	1	2	2	4	...	4	6
Total No. of Aerobes	**74**	**44**	**55**	**84**	**15**	**99**	...

Table 2.—Anaerobic and Facultative Isolates From External Canal and Middle Ear From 68 Patients With Chronic Otitis Media With Perforation

Anaerobic and Facultative	External Canal and Middle Ear Isolates: Present in External Canal Only	External Canal and Middle Ear Isolates: Present in Middle Ear Only	External Canal and Middle Ear Isolates: Present in Both External Canal and Middle Ear	Middle Ear Isolates: Present in Mixed Culture	Middle Ear Isolates: Present in Pure Culture	Middle Ear Isolates: Total No. of Isolates	% of Patients
Anaerobic Gram-positive cocci							
Peptostreptococcus sp	1	6	2	7	1	8	12
Peptococcus sp	3	9	14	22	1	23	34
Anaerobic Gram-positive bacilli							
Bifidobacterium sp	2	4	2	6	...	6	9
Propionbacterium acnes	18	3	2	5	...	5	7
Lactobacillus sp	...	2	2	4	...	4	6
Clostridium sp	...	1	2	3	...	3	4
Gram-negative bacilli							
Fusobacterium nucleatum	...	1	3	4	...	4	6
Bacteroides melaninogenicus	...	4	3	7	...	7	10
Bac fragilis	...	1	4	5	...	5	7
Bac distasonis	...	1	3	4	...	4	6
Bac corrodens	1	...	2	2	...	2	3
Bacteroides sp	...	2	1	3	...	3	4
Total No. of Anaerobes	**25**	**34**	**40**	**72**	**2**	**74**	...
Total No. of Aerobes and Anaerobes	**99**	**78**	**95**	**156**	**17**	**173**	...

monas aeruginosa in seven instances; *Peptococcus* sp in five; *Peptostreptococcus* sp in four; *Bacteroides* sp and *Staphylococcus aureus* in three each; and *Bifidobacterium* sp, *Lactobacillus* sp, and *Haemophilus influenzae* in two each.

Sterility of the canal was achieved in 63 patients (93%). The organisms surviving the procedure of asepsis were considered to present in the external canal only, even when they were recovered from the middle ear. These microbacteria were *Pseud aeruginosa* in three instances, and *S epidermidis* and *Propionbacterium acnes* in two instances each. The data obtained from these patients are given in Tables 1 and 2 as the total number of isolates in a patient, where each bacterial species is counted once even when it was recovered from both ears.

The bacteriological results from the pretreatment aspiration are given in Tables 1 and 2. Bacteria were recovered from all the patients included in

the study. Seventy-eight isolates were recovered only from the middle ear aspirates, 99 only from the external auditory canals, and 95 were present at both sites. For data analysis, only the 173 isolates recovered from the middle ears were considered.

Ninety-five (55%) of the 173 bacterial isolates recovered from the middle ear aspirate were also isolated from the external auditory canal. Seventy-eight (45%) of the middle ear isolates were only recovered from the middle ear aspirate.

There was a total of 99 aerobic and 74 anaerobic isolates recovered from middle ears of the patients. Aerobic bacteria only were isolated in 33 patients (48.5%) and anaerobic organisms only in nine (13.2%). Mixed aerobic and anaerobic isolates were recovered from 26 cases (38.3%). Thus, anaerobes were recovered from 51.5% and aerobes from 86.8% of the patients studied.

The most common bacteria isolated from the middle ear aspirate, in descending order of frequency, were *Pseud aeruginosa* (48.5%), *Peptococcus* sp (34%), *S aureus* (22%), *Bac fragilis* group (13.4%), *Peptostreptococcus* sp (12%), *K pneumoniae* (10.3%), and *Bac melaninogenicus* (10.3%).

In 17 patients (25%), only one isolate (15 aerobic and two anaerobic) were recovered from the middle ear (see Tables 1 and 2). In the rest of the cases, where mixed anaerobic or aerobic bacteria were present the number of isolates ranged from two to five per specimen (average, three isolates per specimen). The combinations of the different isolates varied; there was no consistent pattern of combinations, except between *S aureus* and *Peptococcus* sp, which occurred in six instances.

The predominant organisms recovered from the external auditory canal were *S epidermidis*, *Pro acnes*, and *Pseud aeruginosa*. There was a statistically significant difference noted ($P < .001$) between the isolation rate of *S epidermidis* and *Pro acnes* from the external auditory canal and the middle ear.

Analysis of the data showed no differences between the organisms recovered in the middle ear and the size of the perforation. However, although not statistically significant, more bacteria were present in *both* external canal and middle ear in patients who had large perforation than in those who had a pinhole perforation.

Pseudomonas aeruginosa and *Bacteroides* sp were more frequently recovered in patients who had a perforation for a longer period of time, or in those who had received treatment with more than one course of antimicrobial agents ($P < .05$). No significant statistical correlations were observed between the duration of perforation or the number of courses of antibiotics administered and other bacteria recovered from the middle ear.

COMMENT

The aerobic organisms recovered in this study are similar to those found in previous studies of chronic otitis media,[3-5] where *S aureus*, *Pseud aeruginosa*, and *Proteus* sp were the major pathogens. The lack of proper techniques for isolation of anaerobes may account for the relatively high rate of negative cultures of middle ear effusions in certain previous studies.[3-5] Isolation of anaerobic bacteria from the middle ear fluid of more than half of the patients reinforces studies from the turn of the century, in which a significant role for anaerobes was indicated.[1] Anaerobes were isolated in 33% to 55% of patients with chronic otitis media in studies where anaerobic methodology was used.[6-9]

Anaerobic microorganisms isolated in those studies were *Bacteroides* sp, *Fusobacterium* sp, and Gram-positive anaerobic cocci, all known members of the normal oropharyngeal flora and occasional pathogens of the upper and lower respiratory tract. The polymicrobial bacteriology of chronic otitis media in children was also demonstrated in our study, where aerobic, faculative, and anaerobic bacteria may play a role in the infectious process.

The possible role of anaerobic bacteria in this infection is also suggested by their higher recovery rate from the middle ear only, as compared with their recovery from the external canal. This is more apparent when *Pro acnes* isolates are deleted from the total number of isolates. Thirty-eight anaerobic strains were recovered from the middle ear only, as compared with seven in the external canal.

Only half of the bacteria recovered from the middle ear were also present in the external auditory canal. Furthermore, external ear canal culture in many cases yielded bacteria that were not present in the middle ear. These findings demonstrate that cultures collected from the external auditory canal prior to its sterilization can be misleading. This is particularly important in the case of *Pseud aeruginosa*, which is more frequently recovered in the external auditory canal than in the middle ear. Although this organism is a common inhabitant of the external auditory canal, it can also be recovered from the middle ear, where it may participate in the inflammatory process. Direct middle-ear aspirations through the perforation in the eardrum are therefore more reliable in establishing the bacteriology of chronic otitis media, and can assist in the selection of proper antimicrobial therapy.

Since the methods of isolation and identification of anaerobes were markedly refined and their classification changed, the usage of these techniques provides a clearer assessment of the bacterial flora of chronic otitis media as it is nowadays. The isolation of anaerobes, all known pathogens of the upper and lower respiratory tracts, suggests a possible role for these bacteria in the cause of chronic otitis media.

Nonproprietary Name and Trademark of Drug

Vancomycin hydrochloride—*Vancocin Hydrochloride.*

References

1. Finegold SM: *Anaerobic Bacteria in Human Disease.* New York, Academic Press Inc, 1977, p 117.
2. Sutter VL, Vargo VL, Finegold SM: *Wadsworth Anaerobic Bacteriology Manual*, ed 2. Los Angeles, University of California Press, 1975.
3. Senturia BH, Gessert CF, Carr CD, et al: Studies concerned with tubotympanitis. Ann Otol Rhinol Laryngol 67:440-467, 1958.
4. Jordan R: Chronic secretory otitis media. *Laryngoscope* 59:1002-1015, 1949.
5. Liu YS, Lim DJ, Lang R, et al: Microorganisms in chronic otitis media with effusion. *Ann Otol Rhinol Laryngol* 85(suppl):245-249, 1976.
6. Fulghum RS, Daniel HJ, Yarborough JG: Anaerobic bacteria in otitis media. *Ann Otol Rhinol Laryngol* 86:196-203, 1977.
7. Jokipii MM, Karma P, Ojala K, et al: Anaerobic bacteria in chronic otitis media. *Arch Otolaryngol* 103:278-280, 1977.
8. Brook I, Finegold SM: Bacteriology of chronic otitis media. *JAMA* 241:487-488, 1979.
9. Karma P, Jokipii L, Ojala K, et al: Bacteriology of the chronically discharging middle ear. *Acta Otolaryngol* 86:110-114, 1978.

Measles-Specific Lymphocyte Reactivity and Serum Antibody in Subjects With Different Measles Histories

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• Measles hemagglutination-inhibiting (HAI) antibody titers and measles-specific lymphocyte reactivity were studied in subjects who had previously received killed measles vaccine and had been recently reimmunized with live vaccine—persons who previously had atypical measles, subjects with multiple immunizations with live vaccine, adults with a history of measles, and persons with primary measles immunization. Twelve to 18 months after revaccination of former recipients of killed vaccine, all 31 subjects had measles HAI antibody titers ≥10 and only three had lymphocyte stimulation indices (LSI) >2.8. The mean LSI and geometric mean titer of antibody were similar to those of persons who had had natural measles many years ago. One subject who previously had atypical measles had an HAI titer of <5 and an LSI of 0.5; another had an LSI of 6.0 and an HAI titer of 80. Only one of seven subjects who were immunized more than once with live vaccine had an LSI of >2.8 one year later. The finding of measles-specific lymphocyte reactivity and antibody levels in revaccinated former recipients of killed vaccine that are similar to those in persons who had natural measles suggests that the risk of future atypical measles in this group is slight.

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Atypical measles is a recognized clinical syndrome that occurs following exposure to natural measles in some persons previously immunized with killed measles vaccine.[1-6] Because of the severity of atypical measles, the present national recommendation is to revaccinate all previous recipients of killed measles vaccine,[7,8] even though revaccination is at times accompanied by marked pain, swelling, and erythema at the vaccination site.[9-12] Clinical and laboratory observations suggest that the symptoms of atypical measles and the reactions associated with revaccination of previous killed vaccine recipients both involve the same pathogenic mechanism.[9,13] Recently, we had the opportunity to study 75 previous recipients of killed measles vaccine at the time of revaccination.[9] In this study, we noted that severe local and systemic reactions following revaccination correlated with an exaggerated measles-specific lymphocyte reactivity and low or nonmeasurable measles serum hemagglutination-inhibiting (HAI) antibody titers. These findings in revaccinees supported the earlier observations of Fulginiti et al,[1,12,13] who noted measles skin test positivity in previous recipients of killed vaccine and lack of measurable measles serum antibody in patients at the onset of atypical measles.

In our previous study, revaccination resulted in an antibody response in all subjects with low or undetectable titers in their prevaccination serum samples.[9] However, in three subjects who had severe local reactions at the site of reimmunization, measles-specific lymphocyte stimulation was considerably exaggerated three weeks after revaccination. Since there appears to be a critical balance between the cell-mediated measles-specific immune response and humoral antibody, we have wondered if with increasing time antibody titers in these revaccinated subjects may decrease and the cell-mediated response reciprocally increase, and allow a state of renewed sensitivity to measles virus that on natural exposure would result in atypical measles. In support of this notion is the observation of atypical measles in children who were revaccinated with live vaccine many years after primary killed measles vaccine administration.[5,6]

Since in the past, occasional cases of atypical measles have been noted in persons who as far as could be discerned had received only live vaccine,[14] it has occurred to us that under certain abnormal circumstances, measles-specific lymphocyte sensitization can happen in individuals other than recipients of killed vaccine. Recent trends have led to situations where children have received multiple doses of live vaccine.[15,16] Since one unusual case of measles-associated illness has been reported in a recipient of multiple doses of live measles vaccine,[17] and since we observed an unusual illness in a young, previously vaccinated woman, following reimmunization,[18] we have wondered about the possibility of exaggerated measles-specific lymphocyte reactivity in some multiply vaccinated persons.

To further investigate the aforementioned possibilities, we have performed follow-up measles antibody and measles-specific lymphocyte reactivity studies in the previous participants in our killed measles vaccine-

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revaccination study and in several other subjects with diverse measles histories.

METHODS

Study Participants

Thirty-five adolescents and young adults, the majority of whom participated in our previous study,[9] who received killed measles vaccine more than ten years ago, were studied at various times in relation to reimmunization with live measles vaccine. Thirty-one subjects in this group had studies performed 11 to 18 months after reimmunization. An attempt was made to include as many subjects as possible in this group, who at the time of their revaccination with live vaccine in the previous study had marked local reactions with or without additional systemic symptoms. To qualify as a marked local reaction, persistent pain at the injection site with swelling and/or erythema of several days' duration was necessary.

Also studied were five adolescents and young adults who had initially received killed measles vaccine and who one to four years prior to the present study had had atypical measles; 12 children, adolescents, or young adults who had initially received live measles vaccine and who had had one or two reimmunizations with live measles vaccine during several years' time because of poor antibody responses; nine adults who had had natural measles 17 to 28 years previously; 12 adolescents and young adults with no history of measles or measles immunization and no detectable measles serum antibody (HAI antibody titers <5), eight of whom were administered live measles vaccine and were studied three weeks and one year after vaccination. Written informed consent was obtained from all adult study participants and from the parents of participating children.

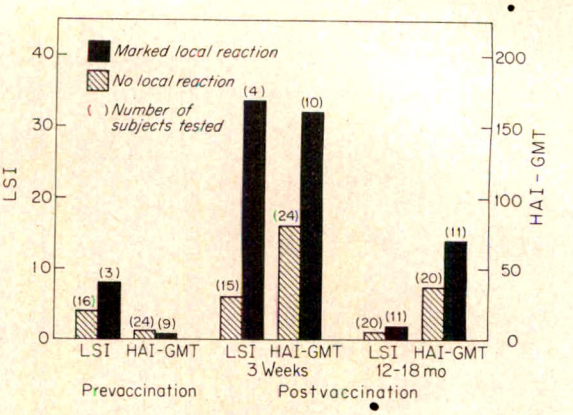
Serologic Techniques

Measles HAI antibody titers were performed on serum by a modification of the method of Hierholzer et al[19] as previously described.[3,5,9,14,15,18,20,21] All titers are expressed as the reciprocals of the serum dilutions.

Lymphocyte Transformation Studies

Lymphocyte transformation studies used commercially available measles complement fixation and control antigens. Methods of lymphocyte separation and harvesting have been previously described.[22] The specific measles-related procedures employed in this study were modified from those of Graziano et al.[23] In brief, 0.2 mL of a 0.5×10^6 lymphocytes/mL solution was incubated in RMPI 1640 medium with 10% fetal calf serum in the presence of 0.02 mL of 1:4 dilution of measles complement fixation antigen, control antigen, no antigen (RMPI medium), or phytohemagglutinin. Because of marked variability of lymphocyte response to different lots of measles antigen, several lots were evaluated. One lot generating adequate response was used in all tests.

After five days, 0.02 mL of tritiated thymidine (100 μCi/mL; specific activity, 20 Ci/μM) was added. Following an 18-hour incubation, the cultures were harvested by means of a multiple-sample harvester. The dried disks were placed in scintillation fluid, counted to obtain the stimulation indices, and the means calculated. Results are reported as lymphocyte stimulation indices (LSI), the ratio of counts per minute of cells incubated with measles antigen to counts per minute of cells incubated with control antigen. A ratio of greater than 2.8 is considered elevated above the background level of the test.



Revaccination with live measles vaccine of former recipients of killed measles vaccine. Measles-specific lymphocyte reactivity expressed as mean lymphocyte stimulation indices (LSI) and geometric mean hemagglutination-inhibiting antibody titers (HAI-GMT) before, three weeks after, and 12 to 18 months after revaccination in subjects with and without marked local reactions at site of reimmunization.

RESULTS

Recipients of Killed Measles Vaccine Who Were Revaccinated

Of the 35 former recipients of killed vaccine enrolled in the present study who were revaccinated previously,[9] 11 had marked local reactions following reimmunization and 24 had no significant reactions. In Fig 1 and Table 1, measles-specific lymphocyte reactivity and HAI antibody titers before, three weeks after, and 12 to 18 months after revaccination are analyzed by the presence or absence of marked local reaction. In both groups—those with marked local reactions and those without—there is a similar lymphocyte reactivity and antibody pattern. Prior to revaccination, the mean LSIs were elevated and the geometric mean titers (GMT) of HAI antibody were low. Three weeks after reimmunization, mean LSI and GMTs increased in both groups, although the rise in LSI in vaccinees without local reactions was less than in vaccinees with marked local reactions. Twelve to 18 months after revaccination, the mean LSI and GMT patterns of the two groups had a reciprocal relationship to prevaccination values. At this point, the mean LSIs were low and the GMTs were about twofold lower than at three weeks, but significantly greater than preimmunization levels.

When LSI and GMT values of subjects with and without marked reactions following revaccination were compared, the following was noted: the LSI was significantly greater before ($P < .05$) and three weeks after ($P < .001$) reimmunization in subjects with reactions than in those without, but these differences had disappeared by 12 to 18 months. The HAI antibody titers were lower initially in those with marked reactions ($P < .05$), increased significantly by three weeks in the same group ($P < .05$), and remained higher at 12 to 18 months ($P < .05$).

Of the total group of former recipients of killed vaccine who were revaccinated, HAI antibody studies were available in 31 subjects at 12 to 18 months of follow up, and in all instances a titer of ≥10 was noted; prior to revaccination, only eight of 33 subjects studied had titers ≥10. Similarly, lymphocyte reactivity data also were available in 31 subjects 12 to 18 months after revaccination, and in 28 instances (90%), the LSIs were <2.8; prior to revaccination, only three of 19 (32%) subjects studied had LSIs <2.8.

Table 1.—Measles-Specific HAI Antibody and Lymphocyte Reactivity* in Subjects With Various Experiences With Measles Virus

Clinical Category	Prior to Live Measles Vaccination or Baseline Value		Three Weeks After Live Measles Vaccination		12 to 18 mo After Live Measles Vaccination	
	Mean LSI	HAI Antibody GMT†	Mean LSI	HAI Antibody GMT	Mean LSI	HAI Antibody GMT
Previous recipients of killed measles vaccine: marked local reaction following live vaccine	7.6 ± 4.1‡ (N = 3)	3.9 (N = 9)	33.4 ± 16.0 (N = 4)	152.0 (N = 10)	1.9 ± 0.4 (N = 11)	70.5 (N = 11)
No or minimal reaction following live vaccine	3.8 ± 0.7 (N = 16)	7.7 (N = 24)	5.9 ± 1.4 (N = 15)	80.0 (N = 24)	1.3 ± 0.9 (N = 20)	37.3 (N = 20)
Atypical measles one to four years prior to present study	1.7 ± 1.0 (N = 5)	20.0 (N = 5)	...	...	...	...
Nonresponders						
Recipients of 2nd dose of live measles vaccine	4.3 ± 1.9 (N = 7)	2.5 (N = 11)	1.5 ± 0.5 (N = 8)	18.3 (N = 10)	2.5 ± 1.5 (N = 5)	2.9 (N = 5)
Recipients of 3rd dose of live measles vaccine	2.7 ± 2.0 (N = 4)	2.5 (N = 4)	10.4 ± 6.2 (N = 4)	10.0 (N = 4)	1.3 ± 0.5 (N = 2)	28.0 (N = 2)
Natural measles 17 to 28 years prior to present study	1.4 ± 0.2 (N = 9)	63.5 (N = 9)	...	...	...	...
Subjects with no history of measles or measles immunization and serum HAI antibody titers of < 5	1.4 ± 0.4 (N = 6)	2.5 (N = 6)	2.2 ± 0.4 (N = 4)	23.8 (N = 4)	1.8 ± 0.3 (N = 6)	8.8 (N = 6)

*Expressed as the lymphocyte stimulation index (LSI); counts per minute (CPM) with measles antigen/CPM with control antigen; HAI indicates hemagglutination-inhibiting antibody.
†GMT indicates geometric mean titer.
‡Standard error of the mean.

Table 2.—Hemagglutination-Inhibiting (HAI) Antibody Titers and Measles-Specific Lymphocyte Stimulation Indices (LSI) in Subjects Vaccinated More Than Once With Live Measles Vaccine

Subject	Prior to Revaccination		Three Weeks After Revaccination		One Year After Revaccination		Three Weeks After Second Revaccination		One Year After Second Revaccination	
	LSI	HAI Antibody Titer	LSI	HAI Antibody Titer	LSI	HAI Antibody Titer	LSI	HAI Antibody Titer	LSI	HAI Antibody Titer
1	2.2	< 5	0.1	20	...	...	...	...	...	...
2	2.0	< 5	1.1	20	...	...	...	...	...	...
3	6.0	< 5	1.2	10	...	...	...	...	...	...
4	...	< 5	0.7	80	...	...	...	...	...	...
5	1.8	< 5	0.4	40	1.8	5	...	...	...	...
6	1.0	< 5	5.3	10	...	...	...	...	...	...
7	15.5	< 5	1.6	40	...	...	...	...	...	...
8	...	...	...	< 5	0.5	< 5	13	40	1.8	20
9	...	< 5	...	...	0.5	< 5	0.2	< 5	...	...
10	...	< 5	...	...	8.6	< 5	1.8	10	...	...
11	...	< 5	...	< 5	1.0	< 5	26.9	10	0.8	40
12	1.2	< 5	1.3	< 5	...	...	...	...	...	...

Former Recipients of Killed Measles Vaccine Who Previously Had Atypical Measles

Lymphocyte and antibody studies were not available prior to the development of atypical measles in the five subjects studied. One subject was evaluated seven days after onset of the disease. He had an initial HAI antibody titer of 10, which increased to ≥1,280 during the acute illness and fell to 20 eighteen months later. The LSI at seven days was elevated to 9.6 and decreased to 0.4 at 18 months. Of the five subjects with atypical measles evaluated at one year or more after their illnesses, four had HAI antibody titers of ≥20, while one had a titer of <5; the latter subject had an LSI of 0.5. The mean follow-up LSI of the five subjects was 1.7 ± 1.0 (Table 1), with only one of the five being >2.8. The LSI in this latter study participant was 6.0 and the HAI antibody titer was 80.

Subjects Vaccinated More Than Once With Live Measles Vaccine

In this category, there were 12 subjects. Eleven of the 12 participants had HAI antibody titers performed prior to a second live measles vaccination and were found to have values of <5. The remaining subject was not studied before reimmunization, but was noted to have an HAI antibody titer of <5 three weeks after revaccination. Measles-specific antibody and

lymphocyte responses following revaccination are given in Tables 1 and 2. Three of ten subjects studied three weeks after revaccination still had HAI antibody titers of <5, and the two subjects of the original 12 not studied three weeks after reimmunization were found to have HAI antibody titers of <5 one year later.

Prior to reimmunization with a second live vaccine, the LSIs of two of seven subjects studied were >2.8, and the mean was 4.3 ± 1.9; one year after reimmunization, one of five subjects restudied had an LSI of >2.8. Four study participants who failed to seroconvert after reimmunization were reimmunized a second time (subjects 8 through 11 in Table 2). Three weeks after this third vaccination, two of the four had very high LSIs; one year later, both had measurable HAI antibody titers and LSIs that were <2.8. None of the 12 subjects revaccinated had clinical reactions associated with the reimmunization procedure.

One additional subject was retrospectively studied. This 19-year-old woman had had live measles vaccine with γ-globulin at age 4 years and a second live vaccination at age 9 years.[18] She was revaccinated a third time during a measles epidemic. Pain, swelling, and erythema of four days' duration occurred at the vaccination site, and systemic complaints of cough, coryza, and eye pain persisted for two weeks. Following the generalized symptoms, a pruritic rash occurred, which lasted ten days. One year after this woman's last measles immunization, the LSI was 0.7 and the measles HAI antibody titer was 320.

Subjects Who Had Had Natural Measles

In this group, nine adults who had had measles 17 to 28 years previously were evaluated. All had measles HAI antibody titers ≥10 and none had LSIs >2.8. The mean LSI in this group was 1.4 ± 0.2, with a range of 0.8 to 2.8.

Subjects With No History of Measles or Measles Immunization and Serum HAI Antibody Titer <5

In this category, there were 12 adolescents and young adults, eight of whom were given live measles vaccine. In six subjects in whom measles-specific lymphocyte reactivity studies were performed prior to immunization, the mean LSI was 1.4 ± 0.4, with a range of 0.3 to 2.8. One subject in this group, a 20-year-old man, had an LSI of 2.8. He had no record of either past measles or immunization; unfortunately, this subject did not participate in follow-up studies so that further evaluation was not possible. Six subjects, two of whom were studied prior to immunization, were evaluated one year after immunization. The mean LSI of this group was 1.8 ± 0.3, with none of the indices being >2.8. One participant had an HAI antibody titer of <5 at the one-year follow-up; the LSI in this subject was 1.3.

COMMENT

The study of measles-specific lymphocyte reactivity has resulted in inconsistent results in many laboratories and large differences in LSIs between different investigators. In 1975, Graziano et al[23] reported "a reliable and reproducible system" for the demonstration of specific lymphocyte reactivity. Their method uses autologous plasma in the cell culture system. Since we were initially concerned with the possibility that plasma that might contain measles antibody could alter the test results, we modified the test procedure and used fetal calf serum. This modification considerably reduced the sensitivity of the test, but proved to be satisfactory for our initial studies.[9] In this present trial, it might have been useful to utilize the more sensitive autologous plasma technique so that some reactivity could have been shown in lymphocytes from live virus vaccinees and from persons who had natural disease in the past. However, since our major concern was aberrant responses, it seemed more appropriate to us to use our original method, so that comparisons with our original study could be made.

A key factor in the measurement of specific lymphocyte reactivity and the reason for difficulty in many laboratories is the measles antigen. In general, the test in our laboratory has only been successful with two specific lots of measles CF antigen. It is our understanding that Graziano et al have also noted success with only certain lots of antigen (personal communication, M. R. Mardiney, Jr).

The results of our previous study suggested that the presence of exaggerated measles-specific lymphocyte reactivity in association with low or nonmeasurable levels of serum antibody was important for the occurrence of aberrant reactions on exposure to measles virus.[9] In this regard, the findings in the present study are encouraging. Of the 36 previous recipients of killed measles vaccine who were studied one year or more after revaccination with live measles vaccine or after the occurrence of atypical measles, the mean LSI was only 1.5 ± 0.2, and only three subjects had indices >2.8. These three subjects in this grouping had LSIs that were ≥4, but each also had a serum HAI antibody titer that was ≥40. These findings suggest that in the majority of instances, infection with measles virus in former recipients of killed vaccine leads to a persistent antibody response and the suppression of the exaggerated cell-mediated immune responsiveness.

The persistent elevation of measles-specific LSIs in three study participants indicates the need for continued observation. However, the high levels of serum antibody 12 to 18 months after reimmunization (Table 1 and Fig 1) is encouraging since we noted in the previous study that no participant with a measles HAI antibody titer of >20 had a severe local or systemic reaction following revaccination.[9] If in the future the antibody titers in these subjects decrease to lower levels and lymphocyte reactivity remains elevated, then perhaps there will again be the risk of atypical measles.

One patient who had atypical measles in the past was found to have an HAI antibody titer of <5. The LSI in this instance was only 0.5. While this individual may not be protected against further measles infection, the question of revaccination deserves careful consideration. A severe reaction with reimmunization seems unlikely with an LSI of 0.5; however,

there may be other unidentified mediators that could lead to an aberrant response. On the other hand, recurrent atypical measles would almost certainly be more severe if it were to occur than a reaction associated with vaccine administration. If the overall herd immunity of the population is good, then individuals such as the previously mentioned subject need not be revaccinated.

The group of subjects who received two or three doses of live measles vaccine are unusual in that all were preselected because of an HAI antibody titer of <5 prior to the first or second revaccination. Although one of the four subjects who was studied one year after the second immunization had an elevated LSI of 8.6 and a HAI antibody titer of <5, suggesting possible susceptibility to severe vaccine reaction, no abnormal clinical response occurred after a third immunization. Three weeks later, the LSI was only 1.8 and the HAI antibody titer was 10. This perhaps suggests that in the presence of low or absent antibody, multiple revaccinations with live measles vaccine may not result in serious consequences even though the in vitro cell-mediated immune response is exaggerated. However, a larger group should be studied to verify this. In addition, these studies do not answer the question relating to possible "hypersensitization" since all revaccinees in the study had HAI antibody titers that were <5. In spite of a normal LSI and antibody titer one year after reimmunization in the 19-year-old woman we studied, her vaccine-associated reaction is disturbing. Also cause for concern was the unusual illness in the multiply vaccinated adolescent girl described by St Geme et al.[17]

The observation of an LSI of 2.8 in one young man with a history of neither immunization nor natural measles is worthy of comment. Most probably, this man had previous experience with measles virus even though he was unaware of it. Our recent survey in the student population revealed a poor correlation between history and measles antibody; of 40 subjects who denied vaccine or measles in the past, 88% had measles antibody.[18]

At the present time in the United States, available data would suggest that about 10% of older adolescents are measles-susceptible.[18] This is reflected in recent measles outbreaks in colleges and at military bases.[18,24] We have pointed out that history is unreliable in determining the susceptible individuals in this age group.[18] Therefore, control measures will need to employ a serologic screening program or, alternatively, vaccination of nine immune subjects for each measles-susceptible subject. Our expressed position favors selective immunization on the basis of serologic screening data as the method of choice in reducing the number of susceptible subjects in the older adolescent and young adult group.[18] However, it is our impression that our view is considered impractical by many authoritative persons concerned with immunizations.[25] Since there is no easy solution to the problem, it is quite probable that outbreaks of measles will occur on military bases and in colleges, and mass immunization programs will be used for disease control. We hope these pending situations can be anticipated so that studies of vaccine complications in previously vaccinated and perhaps sensitized persons can be critically evaluated.

References

1. Fulginiti VA, Eller JJ, Downie AW, et al: Altered reactivity to measles virus: Atypical measles in children previously immunized with inactivated measles virus vaccines. *JAMA* 202:1075-1080, 1967.
2. Nader PP, Horwitz MS, Rousseau J: Atypical exanthem following exposure to natural measles: Eleven cases in children previously inoculated with killed vaccine. *J Pediatr* 72:22-28, 1968.
3. Welliver RC, Cherry JD, Holtzman AE: Typical, modified, and atypical measles: An emerging problem in the adolescent and adult. *Arch Intern Med* 137:39-41, 1977.
4. Nichols EM: Atypical measles syndrome: A continuing problem. *Am J Public Health* 69:160-162, 1979.
5. Zahradnik JM, Cherry JD, Rachelefsky G: Atypical measles acquired abroad: Foreign travel and pseudoexotic disease. *JAMA* 241:1711-1712, 1979.
6. Chatterji M, Mankad V: Failure of attenuated viral vaccine in prevention of atypical measles. *JAMA* 238:2635, 1977.
7. *Report of the Committee on Infectious Diseases*. Evanston, Ill, American Academy of Pediatrics, 1977, p 136.
8. Center for Disease Control: Measles prevention. *Morbid Mortal Week Rep* 27:427-437, 1978.
9. Krause PJ, Cherry JD, Naiditch MJ, et al: Revaccination of previous recipients of killed measles vaccine: Clinical and immunologic studies. *J Pediatr* 93:565-571, 1978.
10. Scott TFM, Bonanno DE: Reactions to live-measles-virus vaccine in children previously inoculated with killed-virus vaccine. *N Engl J Med* 277:248-250, 1967.
11. Buser F: Side reaction to measles vaccination suggesting the Arthus phenomenon. *N Engl J Med* 277:250-251, 1967.
12. Fulginiti VA, Arthur JH, Pearlman DS, et al: Altered reactivity to measles virus, local reactions following attenuated measles virus immunization in children who previously received a combination of inactivated and attenuated vaccines. *Am J Dis Child* 116:671-676, 1968.
13. Fulginiti VA, Arthur JH: Altered reactivity to measles virus: Skin test reactivity and antibody response to measles virus antigens in recipients of killed measles virus vaccine. *J Pediatr* 75:609-616, 1969.
14. Cherry JD, Feigin RD, Lobes LA Jr, et al: Atypical measles in children previously immunized with attenuated measles virus vaccines. *Pediatrics* 50:712-717, 1972.
15. Deseda-tous J, Cherry JD, Spencer MJ, et al: Measles revaccination: Persistence and degree of antibody titer by type of immune response. *Am J Dis Child* 132:287-290, 1978.
16. Marks JS, Halpin TJ, Orenstein WA: Measles vaccine efficacy in children previously vaccinated at 12 months of age. *Pediatrics* 62:955-960, 1978.
17. St Geme J, George BL, Bush BM: Exaggerated natural measles following attenuated virus immunization. *Pediatrics* 57:148-150, 1976.
18. Krause PJ, Cherry JD, Deseda-tous J, et al: Epidemic measles in young adults: Clinical, epidemiologic and serologic studies. *Ann Intern Med* 90:873-876, 1979.
19. Hierholzer JC, Suggs MT, Hall EC: Standardized viral hemagglutination and hemagglutination-inhibition tests: II. Description and statistical evaluation. *Appl Microbiol* 18:824-833, 1969.
20. Cherry JD, Feigin RD, Shackelford PG, et al: A clinical and serologic study of 103 children with measles vaccine failure. *J Pediatr* 82:802-808, 1973.
21. Cherry JD, Feigin RD, Lobes LA Jr, et al: Urban measles in the vaccine era: A clinical, epidemiologic, and serologic study. *J Pediatr* 81:217-230, 1972.
22. Cherry JD, Rolfe UT, Dudley JP, et al: Clinical and immunological study of percutaneous revaccination in children who originally received smallpox vaccine subcutaneously. *J Clin Microbiol* 7:158-164, 1978.
23. Graziano KD, Ruckdeschel JC, Mardiney MR: Cell-associated immunity to measles (rubeola), the demonstration of in vitro lymphocyte tritiated thymidine incorporation in response to measles complement fixation antigen. *Cell Immunol* 15:347-359, 1975.
24. Juels C, Walz S, Maples J, et al: Measles and rubella at a military recruit training center—Illinois. *Morbid Mortal Month Rep* 28:147-148, 1979.
25. Rand KH, Reuman PD: Measles: Ready for eradication? *Ann Intern Med* 90:978-980, 1979.

Isotopic Cisternography in Tuberculous Meningitis of Childhood

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• The changes in the CSF circulation and absorption are valuable in the diagnosis and management of tuberculous meningitis. We describe the isotopic cisternographic analysis of 45 children with tuberculous meningitis and 30 children with purulent meningitis. The cisternographic patterns of tuberculous meningitis consist of (1) obliteration of CSF space at the level of basal cisterns or cisterna Sylvii and (2) ventricular entry of radiopharmaceutical without clearing by 24 hours (communicating hydrocephalus). None of the patients with a definite diagnosis of tuberculous meningitis demonstrated a normal CSF flow pattern. Thirty patients with purulent meningitis underwent isotopic cisternography. Sixteen of 30 patients demonstrated a normal CSF flow pattern, 3 had mild hydrocephalus, 6 had obliteration of the subarachnoid space at the level of cisterna Sylvii at either side, 3 had delay of CSF flow, and 2 had abnormal CSF collection due to a posttraumatic dura defect.

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Tuberculous meningitis is still a serious health problem in Turkey. The complications and the mortality have been markedly reduced with the use of antituberculous drugs and steroids.[1-3] The onset of symptoms of tuberculous meningitis is usually acute in infancy and gradual or vague in older children.[2,3] Signs of meningeal irritation may appear relatively late in the disease.[4] Complications in the acute phase and long-term sequelae are related to the stage of the illness at which the therapy is started.[4] A deterioration of the clinical state in tuberculous meningitis may be due to development of vasculitis, which is a common finding, and hydrocephalus. Alleviation of hydrocephalus by the use of a ventriculoatrial shunt reduces the neurologic complications of tuberculous meningitis considerably.[4-6] In order to reach an early decision about the necessity of the surgical procedure, it is essential to examine the dynamics of the CSF. Assessment of the CSF dynamics by means of radioactive material introduced into the subarachnoid space is a convenient method of study.

We report herein the data on CSF flow in tuberculous meningitis and purulent meningitis by use of isotopic cisternography and evaluate the diagnostic value and the benefit of the shunt operaton in tuberculous meningitis patients in whom hydrocephalus has developed.

Table 1.—Positi

	1	2	3	4	5	6	7	8	9	10	11	12
CSF culture positive for acid-fast bacilli				+		+						+
Gastric washing positive for acid-fast bacilli							+		+		+	
Pathologic examination positive for tuberculous meningitis				+								+
Chest x-ray film with miliary appearance				+				+				
Chest x-ray film suggestive of tuberculous meningitis		+	+	+	+	+		+				+
Family history positive for tuberculous meningitis	+	+			+	+			+	+		

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PATIENTS AND METHODS

The first group consists of 45 patients with tuberculous meningitis. Their ages varied from 4 months to 11 years. Nineteen (42%) of them were girls, and 26 (58%) were boys. The diagnosis of tuberculous meningitis was made by clinical history, physical and neurologic findings and CSF examination, evidence of tuberculosis elsewhere in the body, history of contact with tuberculosis, and identification of tubercule bacilli in CSF or in gastric washings. All 45 patients had CSF findings of tuberculous meningitis such as increased number of lymphocytes and elevation of protein content and low glucose value on more than one occasion. Data that are considered positive for

Table 2.—Isotopic Cisternography Findings in Tuberculous and Purulent Meningitis

	Tuberculous Meningitis (45 Cases)	Purulent Meningitis (30 Cases)
Normal CSF Flow	None	16
Delay in the isotope flow	None	3
Obstruction of the isotope flow in the basal cisterns	33 Bilaterally	None
Obstruction of the isotope flow in cisterna Sylvii	12 Bilaterally	6 Unilaterally
Entry of the isotope into the lateral ventricles (communicating hydrocephalus)	45	3
Dura defect	None	2

Fig 1.—Ventricular filling that first appeared in two hours and remained six and 24 hours after intrathecal injection of Tc 99m human serum albumin in typical case of tuberculous meningitis in anteroposterior position.

Fig 2.—No subarachnoid filling was observed with patients in lateral positions.

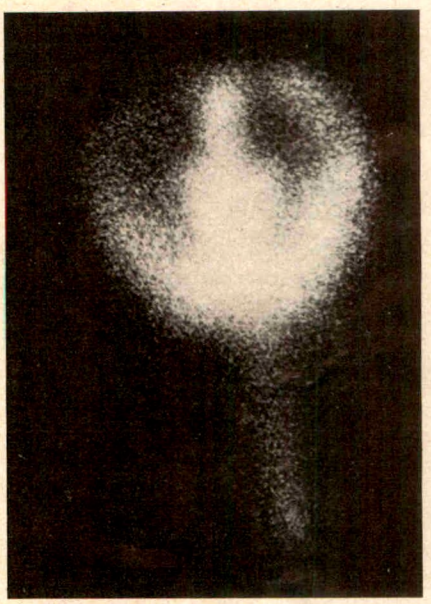

Fig 3.—Anteroposterior view at six hours in case of purulent meningitis: transient filling with early clearance from ventricles and subarachnoid block at level of cisterna Sylvii on right with normal concentration of radioactivity on left parasagittal region.

indings of 45 Patients With Tuberculous Meningitis

Case	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	
		+		+	+	+		+				+	+				+			+			+	+			+	+		+		+	18
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	+			+			+	+								+			+			+		+			+				+	+	19

tuberculous meningitis besides CSF findings are given in Table 1.

The second group consists of 30 patients with bacterial meningitis. Their ages varied from 4 months to 13 years; nine were girls (30%), and 21 were boys (70%). These patients were selected from a group of patients with purulent meningitis who had been improperly treated or who had recurrent meningitis as seen by clinical history, physical examination findings, and laboratory study of the CSF.

Isotopic cisternography studies were carried out on a gamma camera after 1 to 2 μCi of Tc 99m human serum albumin were injected into the lumbar subarachnoid space. Images were taken with the patients in anterior and lateral positions at 2, 6, and 24 hours.

RESULTS

When the radiopharmaceutical is injected intrathecally into the lumbar subarachnoid space, it normally reaches the basal cisterns in one to two hours, the frontal poles and Sylvian fissures in three to six hours, the cerebral convexities by 12 hours, and the sagittal sinus area by 24 hours. Following an intrathecal spinal injection, radioactivity is not normally detected in the ventricular system, probably reflecting the net CSF pathways from the ventricles into the remainder of the CSF space. The radionuclide normally appears to flow into all anatomic structures entered by CSF, except the ventricles.[7-9]

Isotopic cisternograms showed abnormal CSF flow patterns in all of the 45 patients with tuberculous meningitis (Table 2). The findings were as follows: obstruction of the isotope flow in the basal cisterns in 33 cases bilaterally, obstruction of the isotope flow in the cisterna Sylvii in 12 cases bilaterally, entry of the radioisotope into the lateral ventricles without clearing by 24 hours (communicating hydrocephalus) in all of the 45 patients with meningitis (Fig 1 and 2). The observations were made at 2 hours, and no changes were noted at 6 and 24 hours.

Isotopic cisternography was also performed on all patients in the control group with purulent meningitis. The findings of the control group were as follows: normal CSF flow in 16 cases, delay of the isotope flow in 3 cases, obstruction in isotope flow in cisterna Sylvii (unilaterally) in 6 cases (Fig 3), mild hydrocephalus in 3 cases, and dural defect in 2 cases.

COMMENT

Recently, the subarachnoid injection of a radioactive substance for evaluation of CSF flow has received widespread attention. Isotopic cisternography has been used in children for the evaluation of hydrocephalus, CSF leaks, and abnormal communication of the CSF space. Isotopic cisternography is an extremely valuable diagnostic tool in the diseases that may cause abnormal CSF flow.[8,9]

Abnormal CSF flow due to alteration of the structure of the subarachnoid space is probably one of the earliest and most consistent manifestations of tuberculous meningitis.[10] The CSF flow pattern in tuberculous meningitis, which can be demonstrated clearly by isotopic cisternography, has distinct features when compared with normal and purulent meningitis. Obstruction of the isotope flow at the basal cisterns (which occurred in most cases) at the cisterna Sylvii and especially entry of the radioisotope into the lateral ventricles without clearing in 24 hours were the most prominent findings of our studies. None of the patients with a definite diagnosis of tuberculous meningitis demonstrated usual CSF flow. These findings do not correlate with the duration of the illness. Ventriculoatrial shunt was performed on six patients with the cisternographic diagnosis of communicating hydrocephalus due to tuberculous meningitis. Each patient had elevated ventricular pressure, and the CSF protein level was lower than 100 mg/dL. Five of these six patients had an excellent recovery. One patient who was in deep coma prior to operation died a few hours after the shunt procedure.

In the purulent meningitis cases, the purulent material was widely distributed but tended to accumulate over the convexity of the brain into the depth of sulci in the Sylvian fissures and along the major veins and venous sinuses. At the undersurface of the brain, the purulent material was concentrated within the basal cisterns and about the cerebellum. Due to varied clinical presentations, the location of cerebral inflammatory lesions is difficult.[11]

In our study, a normal CSF flow pattern was found in 16 of 30 patients with purulent meningitis. Delay in the CSF flow was found in three cases. In three cases, ventricular entry of radioactive substance with clearing in 24 hours was observed. Six of 30 patients with purulent meningitis had an obstruction in CSF in the cisterna Sylvii unilaterally that was suggestive of subdural effusion. Diagnosis was confirmed as subdural effusions by subdural tap in these patients.

In tuberculous meningitis with communicating hydrocephalus, obstruction of isotope flow at the level of the basal cisterns or cisterna Sylvii were always observed. The different abnormalities in CSF flow patterns can possibly be used in the differentiation of tuberculous meningitis from purulent meningitis by isotopic cisternography.

References

1. Udani PM, Parekh UC, Dustur DK: Neurological and related syndromes in CNS tuberculosis, clinical features and pathogenesis. *J Neurol Sci* 14:341-357, 1971.
2. Udani PM, Bhat SU: Tuberculosis of central nervous system. *Ind Pediatr* 11:7-17, 1974.
3. Weiss W, Flippin HF: The changing incidence and prognosis of tuberculous meningitis. *Am J Med Sci* 250:46-56, 1965.
4. Wilkinson HA, Ferris EU, Muggia AL, et al: Central nervous system tuberculosis: A persistent disease. *J Neurosurg* 34:15-22, 1971.
5. James AE, Hodges FJ, Jordan CE, et al: Angiography and cisternography in acute meningitis due to *Haemophilus influenzae*. *Radiology* 103:601-606, 1972.
6. Butler IJ, Johnson RT: Central nervous system infections. *Pediatr Clin North Am* 21:659-660, 1974.
7. Di Chiro G, Reames PM, Matthews WB: RISA ventriculography and RISA cisternography. *Neurology* 14:185-191, 1964.
8. Heller RM, James AE: Clinical applications of cisternography in the pediatric age group. *Am J Roentgenol Rad Ther* 116:590-597, 1972.
9. Strecker EP, James AE: Evaluation of the changes of cerebrospinal fluid movement associated with meningitis: A cisternographic analysis. *Am J Roentgenol* 118:147-154, 1973.
10. Greenfield JG, Blackwood W, McMenemey WH, et al: *Neuropathology*, ed 2. Baltimore, Williams & Wilkins Co, 1963, p 154.
11. Dodge PR, Swartz MN: Bacterial meningitis. *N Engl J Med* 272:1003-1010, 1965.

Sonographic Diagnosis of Cholelithiasis in Childhood

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• **With the development of new gray scale signal processing, a high level of accuracy has been obtained with gallbladder sonography. Biliary calculi seem to be more prevalent in the pediatric population than is generally appreciated. Two interesting features of childhood cholelithiasis are the increased incidence in patients without hemolytic anemia and the uncommonly high percentage of gallstones visible with plain roentgenograms of the abdomen. Cholecystosonography is offered as an additional method of establishing diagnostic certainty.**

(*Am J Dis Child* 134:575-576, 1980)

Cholelithiasis is more prevalent among the pediatric population than is commonly appreciated.[1-4] It is a frequent misconception that only pediatric patients with hemolytic disorders will exhibit cholelithiasis. Several large series indicate that the majority (a figure in excess of 75%) of children with cholelithiasis do not have a hemolytic disease.[2,5,6] Of course, the incidence of cholelithiasis in children does not approach that of the adult population. Consequently, symptoms readily attributed to cholelithiasis in adults will less frequently be efficiently diagnosed in the pediatric patient in whom there is no hemolytic disorder.

It is of interest that gallstones are more often opaque in children than in adults (50% to 90% vs 20%) and plain roentgenographic studies of the abdomen will often suggest the diagnosis[5,6] (Fig 1). However, as with adults, oral cholecystography will fail in a certain percentage of children with gallbladder disease. Not all of these patients will have roentgenographically visible (opaque) calculi. Although there are circumstances in which the nonvisualizing oral cholecystogram would be sufficient to establish the diagnosis, there may exist a group of patients in whom more diagnostic certainty is required. Cholelithiasis or cholecystitis will be present in 95% of those patients in whom the gallbladder fails to opacify.[7] There are, however, extrinsic causes for nonopacification, such as liver disease, failure to comply with the requirements of the examination, biliary stasis, diarrhea, and malabsorption. Also, some patients have a known or suspected allergy to iodinated compounds such as would be used for an oral cholecystogram.

With this in mind, an ancillary, or even alternate, method of detection currently widely accepted in establishing the diagnosis of cholelithiasis in adults is ultrasound. As ultrasonic interrogation depicts anatomy independently of function, the nonvisualizing gallbladder (hidden to the radiologist) can be viewed on the sonogram and a statement regarding the presence or absence of calculi can be made rather than inferred. An overnight fast is recommended to assure maximal distention of the gallbladder (this can be dispensed with in the acute situation), but no further preparation is necessary except for sedation of infants and young toddlers.

The normal gallbladder is readily detected as an echo-free structure

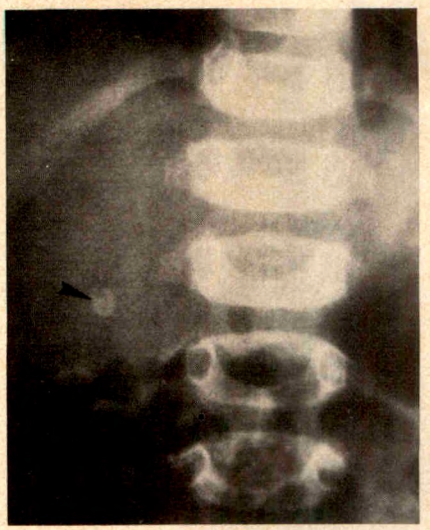

Fig 1.—A 16-month-old female infant with congenital heart disease. Arrowheads indicate two calcified gallbladder calculi.

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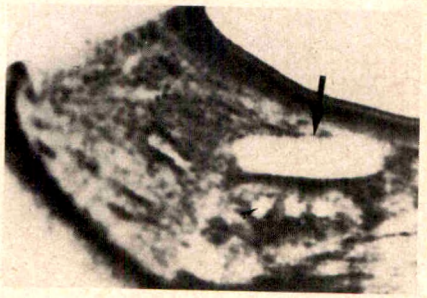

Fig 2.—Sagittal sonogram of right upper quadrant of 11-year-old child. Section is 5 cm to right of midline. Gallbladder (arrow) lies anterior to kidney. (Arrowhead points to renal pyramid.)

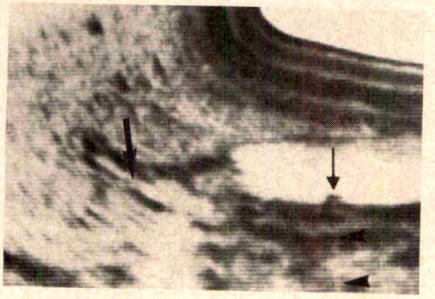

Fig 3.—Sagittal sonogram of right upper quadrant of 7-year-old boy with hereditary spherocytosis. Section was taken to right of midline. Tiny 4-mm calculus (small arrow) casts a faint acoustic shadow (arrowheads). Plain roentgenogram was normal. Large arrow indicates portal vein.

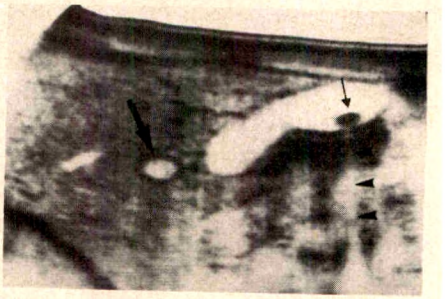

Fig 4.—Sagittal sonogram of right upper quadrant of 16-year-old boy. Small arrow indicates gallstone; arrowheads define acoustic shadow. Plain roentgenogram displayed single, dense calcification within right upper quadrant. Large arrow indicates portal vein.

within the right upper quadrant. It is located just inferior to the free edge of the liver, often immediately anterior to the right kidney (Fig 2). Sonographic detection of calculi (in capable hands) now approaches an accuracy greater than 95%.[8-10] Stones as small as 3 mm can be displayed. The three principal criteria for establishing the diagnosis are a reproducible echogenic focus within the gallbladder lumen, gravity-dependent layering, and a posterior "acoustic shadow" (Fig 3).

An echogenic focus is the sonographic term used to describe the biliary calculus. The size and internal consistency will be recorded as a well-defined cluster of echoes within the echo-free bile. This same cluster of echoes (calculus) can be demonstrated to move into the more dependent position of the gallbladder as the patient is placed in various positions (eg, upright, decubitus).

The curious posterior "acoustic shadow" is a result of the high attenuation of the ultrasound beam by the dense gallstone. This attenuation will result in an absence of sound (ie, an acoustic shadow) beneath the intraluminal stone. Initial work indicated that the shadow was a function of stone size. All stones longer than 3 mm displayed the phenomenon and the demonstration of the posterior shadow was found to be independent of calcium content, shape, surface characteristics, or specific gravity of the stone (Fig 4).[11]

Recent in vitro work has shown that all gallstones will cast an acoustic shadow, regardless of size. However, the production of the shadow was highly dependent on the relationship between the stone and the acoustic-beam width. If the peripheral edge of the acoustic beam encounters the stone, such that a portion of the stone is not within the image obtained, no shadow will be seen. Additionally, if the beam width was wider than the stone diameter, no shadow was perceived.[12] As expected, these variables are easier to control in the experimental situation than in the standard clinical setting. Although all three features may not be evident in every case, the presence of all three assures a diagnosis of cholelithiasis with 100% accuracy.[9] All need not be present for one to be equally confident about the diagnosis.

This series of patients is not large enough to make any reliable statistical analysis of the accuracy of cholecystosonography for children. Among the five patients we have examined with congenital spherocytosis, only that patient whose sonogram is depicted in Fig 3 was found to have gallstones. The exclusion of stones in the remaining cases was made by palpation and inspection at surgery. Our accuracy in a series of 103 adult patients is 98%, with 1% false-negative and 1% false-positive results. The sonographic examination of the gallbladder of children is the same as of an adult. However, as sonography requires skin contact, sedation of those in the younger age group will be necessary and cannot be dispensed with in the uncooperative child.

References

1. Hanson BA, Mahour GH, Woolley MM: Disease of the gallbladder in infancy and childhood. *J Pediatr Surg* 6:277-283, 1971.
2. Strauss RG: Cholelithiasis in childhood. *Am J Dis Child* 117:689-692, 1969.
3. Crichlow RW, Seltzer MH, Jannetta PJ: Cholecystitis in adolescents. *Am J Dig Dis* 17:68-72, 1972.
4. Piretti R, Auldist A, Stephens C: Acute cholecystitis in children. *Surg Gynecol Obstet* 140:16-18, 1975.
5. Moossa AR: Cholelithiasis in childhood. *J R Coll Surg Edinb* 18:42-46, 1973.
6. Harned RK, Babbitt DP: Cholelithiasis in children. *Radiology* 117:391-393, 1975.
7. Mugahed Z, Evans SA, Whalen JP: Non-opacified gallbladder on oral cholecystography. *Radiology* 122:1-3, 1974.
8. Bartrum RJ, Crow HC, Foote SR: Ultrasonic and radiographic cholecystography. *N Engl J Med* 216:538-541, 1977.
9. Crade M, Taylor KJW, Rosenfeld AT, et al: Surgical and pathologic correlation of cholecystosonography and cholecystography. *Am J Roentgenol* 131:227-229, 1978.
10. Leopold GR, Amberg J, Gosink BB: Gray scale ultrasonic cholecystography: A comparison with conventional radiographic techniques. *Radiology* 121:445-448, 1976.
11. Carroll BA: Gallstones: In vitro comparison of physical, radiographic, and ultrasonic characteristics. *Am J Roentgenol* 131:223-226, 1978.
12. Filly RA, Moss AA, Way LW: In vitro investigation of gallstone shadowing with ultrasound tomography. *J Clin Ultrasound* 7:255-262, 1979.

Endocarditis in the Newborn

Gail A. McGuinness, MD; Richard M. Schieken, MD; Grace F. Maguire, MD

• Three cases of endocarditis confirmed at autopsy were identified in an intensive care nursery during an eight-month period. Echocardiography demonstrated abnormal echoes in the region of the mitral valve in one infant and the tricuspid valve in the other two infants. Both the diverse clinical manifestations of bacterial and nonbacterial endocarditis and the value of echocardiography in the establishment of an antemortem diagnosis are discussed. This previously unusual entity seems to be occurring with greater frequency in neonatal intensive care units that provide vigorous efforts to support severely ill infants.

(*Am J Dis Child* 134:577-580, 1980)

Endocarditis in the neonate has been considered to be an exceedingly rare disease. Prior to the antibiotic era, bacterial endocarditis was a known complication of septicemia in the neonate, usually identified on postmortem examination without the supporting evidence of cultures or Gram's stains.[1] During an hiatus of almost 20 years, the literature yields few reports of neonatal bacterial endocarditis and, only recently, this entity has again been observed in intensive care nurseries.[2,3] In addition, silent aseptic cardiac valve thrombosis has been reported,[4] especially in infants who have been asphyxiated.

We are reporting three cases of endocarditis identified in our nursery during an eight-month period. Echocardiography demonstrated abnormal echoes in the region of the mitral valve in one infant and the tricuspid valve in the other two. These abnormalities were subsequently proved to be indicative of vegetations on postmortem examination. We believe this to be the first report of tricuspid valve endocarditis diagnosed in the newborn by echocardiography. Moreover, we wish to call attention to the protean manifestations of both bacterial and nonbacterial endocarditis in the newborn infant and to report the diverse factors that predispose towards this disease.

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METHODS

Echocardiograms were performed using an ultrasonoscope with a 5-mHz unfocused transducer. M-mode scans were performed from the apex of the left ventricle to the aortic root. The transducer was then repositioned to image sequentially the tricuspid and pulmonic valves.

Bacterial cultures of blood, urine, and CSF were obtained from each infant when clinically indicated prior to starting antibiotic therapy. Cultures were processed by the usual methods[5] by the hospital's Clinical Microbiology Laboratory. Antimicrobial sensitivities were performed by broth dilution.[5]

REPORT OF CASES

Case 1.—This 1,080-g female infant was born after a 26 weeks' gestation and had severe respiratory distress syndrome requiring ventilatory assistance. She was weaned from the respirator after several days, but she never tolerated feedings by nasogastric tube. At 2 weeks of age, a central venous line was placed in the right internal jugular vein and positioned in the superior vena cava for the administration of parenteral nutrition. Two weeks later, episodes of bradycardia and apnea required the reinstitution of ventilatory support. A blood culture obtained from the central venous line showed *Staphylococcus epidermidis* growth, and the infant was begun on a regimen of methicillin sodium. Despite catheter removal, blood cultures continued to show *Staph epidermidis* growth. The infant was transferred to our hospital at 7 weeks of age.

At the time of admission, the child weighed 1,300 g, was malnourished, jaundiced, and in severe respiratory distress. There was a grade 2/6 midsystolic murmur heard best at the lower sternal border. The liver and spleen were palpable to the pelvic brim.

Laboratory data indicated the following values: hemoglobin, 7.4 g/dL; hematocrit, 24%; WBCs, 10,000/cu mm, with 78% neutrophils. The peripheral blood smear revealed many burr cells, schistocytes, and toxic granulations. Platelet count was 8,000/cu mm. Total serum bilirubin level was 12.5 mg/dL, with a direct component of 10.7 mg/dL. The SGOT determination was 210 IU/L, the SGPT determination was 68 IU/L, and the alkaline phosphatase level was 212 IU/L. A chest roentgenogram indicated a normal-sized heart and severe bronchopulmonary dysplasia. An ECG was within normal limits, and an echocardiogram demonstrated a mass in the right atrium attached to the tricuspid valve.

From the time of the infant's admission until death, nine blood cultures had *Staph epidermidis* growth. The minimal inhibitory concentrations to this organism were: ampicillin sodium, 16 μg/mL; cephalothin sodium, 1 μg/mL; chloramphenicol sodium succinate, 4 μg/mL; clindamycin phosphate, > 16 μg/mL; erythromycin lactobionate, 16 μg/mL; methicillin sodium, 8 μg/mL; penicillin G potassium, 16 μg/mL; and vancomycin hydrochloride, 2 μg/mL. Methicillin therapy was discontinued and cephalothin sodium usage begun in a dose of 300 mg/kg/day. While receiving this dose of cephalothin, the serum inhibitory levels were less than 1:2 three hours after drug administration. While receiving 400 mg/kg/day divided every two hours, serum inhibitory and bactericidal levels were 1:16 two hours after administration. The CSF and urine cultures remained negative.

Despite vigorous antimicrobial therapy as just outlined, blood cultures continued to yield *Staph epidermidis* growth. The infant had extensive fissuring and sloughing of the skin, cultures of which had a growth of *Serratia* sp. Hypotension and hypothermia refractory to supportive therapy developed and she died at 11 weeks of age.

The tricuspid valve was thickened and uneven and there was a 10 × 15-mm deep red fibrous vegetation that spanned the plane of the valve orifice

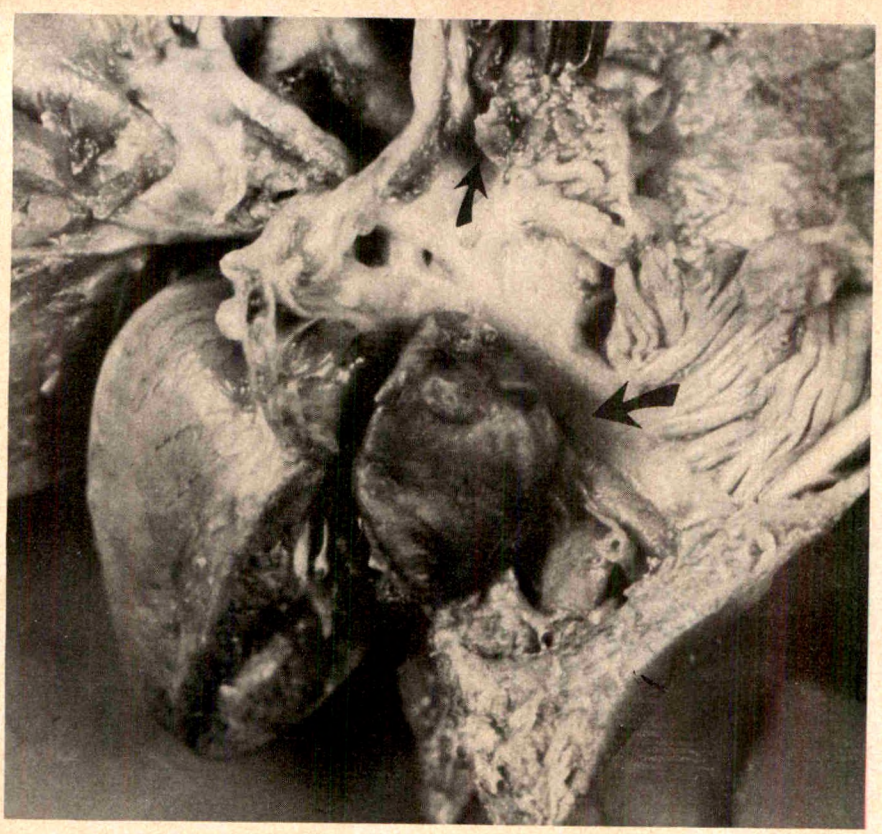

Fig 1.—Large fibrous vegetation spans tricuspid valve orifice (large arrow). Superior vena cava contains mural thrombus extending from vegetation within right atrium (small arrow) (case 1).

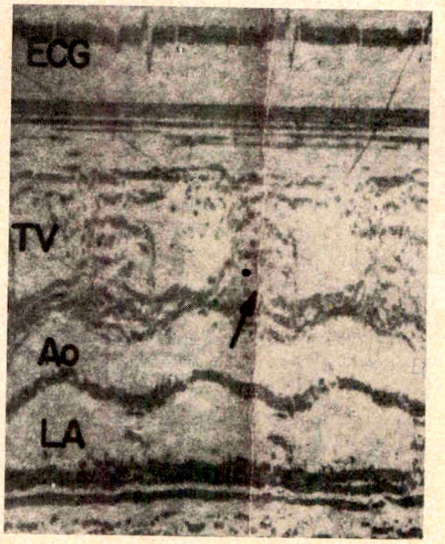

Fig 2.—Echocardiogram. Dense cloud of echoes (arrow) most prominent during diastole appears attached to tricuspid valve (case 1).

(Fig 1). The superior vena cava contained an endothelialized mural thrombus 15 mm in length that extended to the orifice of the vena cava within the right atrium. The tricuspid vegetation consisted mainly of dense fibrin aggregates and hyaline material with few neutrophils and many Gram-positive cocci.

The liver occupied about half of the abdominal volume. Hepatocytes showed degeneration and pyknosis. A ring of dense fibrous tissue surrounded most central veins. The spleen was enlarged, soft, and congested. On microscopic examination, Malpighian corpuscles were not seen.

Postmortem blood cultures showed growths of a mixture of *Staph epidermidis* and a *Serratia* sp. Lung tissue also had growth of *Serratia*, though in small yield. Gram-negative sepsis was never clinically recognized in this infant. However, her extensive skin lesions provided an obvious portal of entry, and it is probable that *Serratia* septicemia contributed to her death.

The echocardiogram disclosed normal dimensions of all chambers and flat septal motion. A dense cloud of echoes appeared attached to the tricuspid valve most prominent during diastole (Fig 2). This was reproducible on several echocardiograms.

CASE 2.—This 2,000-g female infant was born at 36 weeks' gestation after oxytocin augmentation of labor because of maternal eclampsia. Late decelerations of the fetal heart rate were noted, and a cesarean section was performed. The infant was profoundly depressed at birth, requiring intubation and resuscitation. Cultures of the blood, CSF, and urine were obtained, and she was given ampicillin and kanamycin sulfate. She was transported to our hospital seven hours after birth. On admission, the infant had an umbilical artery catheter in place, with the tip at the sixth thoracic vertebra. An umbilical vein catheter had been inserted at the time of delivery for resuscitation and was subsequently removed.

On physical examination, she had a grade 2/6 holosystolic murmur at the left lower sternal border. A gallop rhythm was present, and the liver was palpable 1½ cm below the right costal margin. Chest roentgenogram depicted hyaline membrane disease with cardiomegaly. The ECG showed ST segment changes, and an echocardiogram revealed a left atrial-aortic root ratio of 2:1, with a dense cloud of echoes beneath the mitral valve consistent with a vegetation. This abnormality was recognized premortem, but serious consideration was not given to the diagnosis of endocarditis because of its rarity in the newborn. Therapy with digoxin and furosemide was begun.

Her course was further complicated by acute renal failure. On the fifth day of life, the infant had a bulging fontanelle and a decrease in the hematocrit reading, and she became flaccid and unresponsive. She died shortly thereafter. Subsequently, a blood culture obtained at the local hospital yielded *Escherichia coli* growth.

A clot was present in the umbilical vein. There were multiple 3- to 4-mm vegetations on the mitral valve leaflets (Fig 3). Microscopically, Gram-positive cocci in clumps, as well as neutrophils, were noted within the fibrinous vegetations. There were areas of coagulation necrosis and hemorrhage in the anterior papillary muscle of the left ventricle. The lungs showed widespread atelectasis and hemorrhage along with hyaline membranes. Hepatocytes contained multiple clear vacuoles.

The kidneys showed multiple hemorrhagic infarcts bilaterally. On microscopic examination, there was a large area of coagulation necrosis in the medulla of the left kidney. Cultures of the blood, lung, and kidney infarct obtained at autopsy had growths of *Staph epidermidis*.

CASE 3.—This 2,500-g female infant was born at 43 weeks' gestation. At birth, the

Fig 3.—Multiple 3- to 4-mm vegetations (arrows) are adherent to mitral valve (case 2).

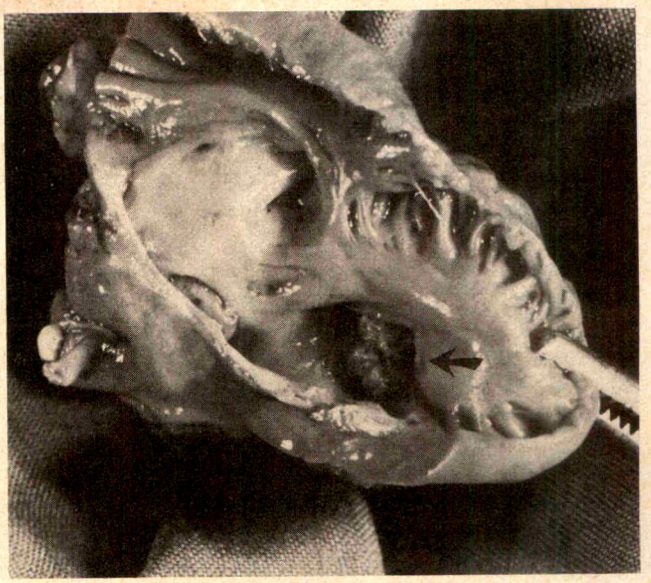

Fig 4.—Irregular vegetation (arrow) is seen on atrial side of posterior and right lateral tricuspid valve leaflets (case 3).

infant was covered with thick meconium and required intubation in the delivery room. On intubation, the vocal cords appeared clean, and no meconium could be suctioned from below the cords. Apgar scores were 2 and 5 at one and five minutes.

For the next several hours, she was free of respiratory distress and tolerated an initial feeding. The initial chest roentgenogram revealed coarse bilateral infiltrates and a normal-sized heart. Cultures of the blood, CSF, and urine were obtained, which were subsequently negative. The infant was begun on a regimen of ampicillin and kanamycin. At 7 hours of age, she was noted to have a respiratory rate of 128/min. Cardiac examination failed to disclose a murmur or gallop. The second heart sound was increased in intensity. The peripheral pulses were diminished. The lung fields were clear to auscultation. A repeated chest roentgenogram showed clearing of the initial infiltrates and a normal-sized heart.

During the next ten hours, the infant's respiratory distress worsened, and ventilatory assistance was instituted. A temporal artery line was established. An echocardiogram was interpreted as normal; however, congenital heart disease and persistent fetal circulation were still considered diagnostic possibilities.

Because of her deteriorating condition and persistent hypoxemia, cardiac catheterization was undertaken at 20 hours of age. The catheter was placed into the left atrium. A single injection was performed to rule out transposition of the great vessels. This demonstrated a normal-sized left ventricle and a normally positioned aorta. Left atrial blood was desaturated. Because of the infant's critical condition, no attempts were made at delineating right-sided cardiac anatomy. After the catheterization, the infant's condition continued to deteriorate rapidly, with acidosis, hypoxia, and hypotension unresponsive to therapy. She died at 32 hours of age. When the echocardiogram was reviewed retrospectively, evidence of a tricuspid valve vegetation was noted.

There was an irregular yellow-white 2 × 3-mm vegetation on the atrial side of the tricuspid valve leaflets (Fig 4). This growth overlay the tricuspid valve and obstructed atrial to ventricular blood flow. Microscopic examination showed no disruption of the valvular endothelium. The overlying vegetation was composed of a bland, hyaline, unorganized thrombus that stained positively for fibrin. Enmeshed within the vegetation were occasional neutrophils, lymphocytes, and RBCs. No bacteria, fungi, or inflammatory foci were noted. Cultures of the valvular vegetation as well as heart blood were negative. All sections of the lungs revealed multiple occlusive fibrin thromboemboli in the small pulmonary arteries and arterioles that were morphologically similar to the tricuspid growth.

COMMENT

Although neonatal endocarditis has been infrequently recognized in the past, its incidence may be increasing because of our ability to support critically ill infants.[2-4] Two recent reports implicated the use of umbilical and central venous catheters in the etiology of both septic and aseptic endocarditis.[2,3] The causative event may be endocardial injury from venous catheters within both left and right atria resulting in the adherence of platelets and fibrin, which leads to the formation of a thrombotic vegetation. Both embolic phenomena and secondary infection of the vegetation, especially with *Staph aureus* and *Staph epidermidis*, were common.

There are only a few reports of bacterial endocarditis in neonates as a complication of septicemia if one requires both histologic and bacteriologic confirmation of the diagnosis. Most of these well-documented cases are in infants with associated congenital heart disease[6-8] although there are rare occurrences in infants without underlying structural anomalies of the heart.[8-10] Vegetations have occurred on the mitral valve, the endocardium of the right and left atria, and the right ventricular septum. Responsible organisms most frequently identified are *Staph aureus*, *Streptococcus pneumoniae*, and β-hemolytic *Streptococcus*. In most of these cases, infective endocarditis was masked by the effects of overwhelming infection such as meningitis or omphalitis so that an antemortem diagnosis was not made.

More recently, attention has been drawn to acute, verrucous, nonbacterial endocarditis in the newborn. Favara et al[4] reported a syndrome of dis-

seminated intravascular and vegetative cardiac thrombosis identified at postmortem examination in 24 infants. It is characterized by thrombosis and cardiac valve platelet masses involving the tricuspid and mitral valve in about equal proportions. This syndrome seems to be confined to the mortally ill newborn with severe hypoxia. Death occurs in the first several days of life, and in some cases, as early as 12 hours after birth. Other investigators have reported similar cases.[11-14]

The three patients described herein demonstrate the diverse causes and manifestations of endocarditis in the neonatal period. One patient (case 1) was of extremely low birth weight and had tricuspid valve endocarditis secondary to a catheter placed in the right superior vena cava for parenteral nutrition, which may have served as a nidus for infection with *Staph epidermidis*. A second patient (case 2) with hyaline membrane disease had *E coli* sepsis and congestive heart failure, subsequently found to be due to mitral valve endocarditis. Complications included renal emboli and secondary infection of the mitral valve with *Staph epidermidis*. The third patient (case 3) was asphyxiated at birth and died at 32 hours of age of progressive hypoxemia unresponsive to mechanical ventilation. At postmortem examination, tricuspid valve nonbacterial endocarditis was identified, with the cause of death being diffuse pulmonary emboli.

The clinical diagnosis of endocarditis in the young infant is exceedingly difficult. As demonstrated by our patients, the presence or absence of a murmur and/or heart failure was not helpful, nor was the chest roentgenogram or ECG. The diagnosis would not have been suspected in these infants without the use of the echocardiogram. Though antemortem diagnosis was made in two of our three patients, in case 3, endocarditis was only identified after death and the vegetation was seen only on retrospective review of the echocardiogram. Two cases of mitral valve endocarditis in young infants diagnosed by echocardiogram have been reported.[15,16] Our additional cases of both tricuspid and mitral valve endocarditis support the value of this noninvasive method to establish the diagnosis.

Echocardiography is safe and can be easily and rapidly performed in the sickest of infants in a neonatal intensive care unit.[17] Echocardiographic demonstration of vegetations in adult patients with bacterial endocarditis was first reported in 1973.[18] The sensitivity of this procedure is related to the size of the vegetation. A study in adults indicated that echocardiography can detect vegetations provided that they are at least 2 mm in diameter.[18] The typical appearance of a vegetation on echocardiography is that of an uneven or irregular thickening of the valve, often with a mass of shaggy or fuzzy echoes attached to the leaflet. Despite this apparent thickening, the motion of the valve is unrestricted.[19] In adults, the echocardiogram has been useful as a prognostic indicator in that patients with vegetations large enough to be documented by this technique have a poor prognosis with medical treatment.[20] Most such patients either die or require operative intervention.

Aggressive and appropriate antibiotic therapy was not successful in case 1. Failure to sterilize the blood suggests that the mural thrombus was acting as a foreign body and continually seeding the bloodstream. Surgical removal of the thrombus was not considered to be a reasonable alternative because of the extremely low birth weight and critical condition of the infant. These cases suggest that endocarditis in the newborn may have an unfavorable prognosis despite antibiotic therapy. Whether surgery has a role to play in the treatment of such infants, as it does in the adult and older child, is unknown.

These three infants demonstrate that endocarditis can manifest itself as a multisystem disease with cardiac, pulmonary, hepatic, hematologic, and renal involvement. The clinician should suspect both septic and aseptic endocarditis in neonates with indwelling catheters, underlying septicemia, and severe hypoxemia and hypotension so that attempts at diagnosis can be undertaken. Echocardiography may provide some information regarding the incidence and natural history of this entity, which seems to be increasing in frequency in neonatal intensive care units.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*
Cephalothin sodium—*Keflin.*
Oxytocin—*Pitocin, Syntocinon, Uteracon.*
Vancomycin hydrochloride—*Vancocin Hydrochloride.*

References

1. Macaulay D: Acute endocarditis in infancy and early childhood. *Am J Dis Child* 88:715-731, 1954.
2. Symchych PS, Krauss AN, Winchester P: Endocarditis following intracardiac placement of umbilical venous catheters in neonates. *J Pediatr* 90:287-289, 1977.
3. Edwards K, Ingall D, Czapek E, et al: Bacterial endocarditis in four young infants. *Clin Pediatr* 16:607-609, 1977.
4. Favara BE, Franciosi RA, Butterfield LJ: Disseminated intravascular and cardiac thrombosis of the neonate. *Am J Dis Child* 127:197-204, 1974.
5. Lennette EH, Spaulding EH, Truant JP: *Manual of Clinical Microbiology.* Washington, DC, American Society for Microbiology, 1974.
6. Moodie DS, Gallen WJ: Pneumococcal endocarditis in a 7-week-old infant: A case complicated by congenital heart malformation with mitral valve perforation. *Am J Dis Child* 129:980-983, 1975.
7. Blieden LC, Morehead RR, Burke B, et al: Bacterial endocarditis in the neonate. *Am J Dis Child* 124:747-749, 1972.
8. Johnson DH, Rosenthal A, Nadas AS: Bacterial endocarditis in children under 2 years of age. *Am J Dis Child* 129:183-186, 1975.
9. Lewis IC: Bacterial endocarditis complicating septicaemia in an infant. *Arch Dis Child* 29:144-146, 1954.
10. Zakrzewski T, Keith JD: Bacterial endocarditis in infants and children. *J Pediatr* 67:1179-1193, 1965.
11. Kunstadter RH, Kaltenekker F: Acute verrucous endocarditis in the newborn. *J Pediatr* 61:58-64, 1962.
12. Oppenheimer EH, Esterly JR: Nonbacterial thrombotic vegetations: Occurrence in neonate, infant, and child, and relation to valvular lesions in cardiac defects. *Am J Pathol* 53:63-81, 1968.
13. Liwnicz BH, Lepow H: Nonbacterial thrombotic endocarditis in premature child. *NY State J Med* 76:912-916, 1976.
14. Ward AM: Endocarditis in the neonatal period. *Arch Dis Child* 46:731-733, 1971.
15. Weinberg AC, Laird WP: Group B streptococcal endocarditis detected by echocardiography. *J Pediatr* 92:335-336, 1978.
16. Bender RL, Jaffe RB, McCarthy D, et al: Echocardiographic diagnosis of bacterial endocarditis of the mitral valve in a neonate. *Am J Dis Child* 131:746-749, 1977.
17. Grossman H, Felman A, Kirkpatrick JA, et al: Ultrasonography in children. *Pediatrics* 54:480-481, 1974.
18. Dillon JC, Feigenbaum H, Koneke LL, et al: Echocardiographic manifestations of valvular vegetations. *Am Heart J* 86:698-704, 1973.
19. Roy P, Tajik AJ, Giuliani ER, et al: Spectrum of echocardiographic findings in bacterial endocarditis. *Circulation* 53:474-482, 1976.
20. Wann LS, Dillon JC, Weyman AE, et al: Echocardiography in bacterial endocarditis. *N Engl J Med* 295:135-139, 1976.

Encephalopathy in Young Children With Moderate Chronic Renal Failure

James F. Bale, Jr, MD; Richard L. Siegler, MD; Patrick F. Bray, MD

• We studied three boys who had a similar encephalopathy develop during moderate chronic renal failure. The features included cerebellar system dysfunction, seizures, and intellectual and motor retardation. Extensive laboratory investigation failed to disclose an etiology other than chronic azotemia. These cases suggest that the developing nervous system is particularly sensitive to the effects of chronic azotemia. Early dialysis and/or transplantation should be considered in such children in an attempt to modify the serious nervous system abnormalities.

(*Am J Dis Child* 134:581-583, 1980)

The neurologic complications of chronic renal failure are numerous and include polyneuropathy and encephalopathy.[1-4] Although such complications are common, they often correlate poorly with the severity of azotemia.

We studied three boys with moderate chronic renal failure who had a similar constellation of neurologic signs and symptoms. The features included ataxia, hypotonia, intellectual retardation, and minor motor and grand mal seizures. Despite extensive laboratory investigations, no etiology other than chronic azotemia was identified.

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Reprints not available.

REPORT OF CASES

Case 1.—A male infant was the 3,520-g product of an uncomplicated term pregnancy and delivery. The immediate neonatal course was without complications. His subsequent growth was poor, and at 2½ months of age, he weighed only 3,500 g. Examination disclosed a poor urinary stream, and the diagnosis of posterior urethral valves was made. He underwent valve resection but later required multiple surgical procedures including ureteral reimplantation, placement of nephrostomy tubes, suprapubic tube drainage, and cutaneous ureterostomy. Despite these procedures, he remained hydronephrotic and had multiple urinary tract infections and persistent azotemia, with BUN and serum creatinine concentrations ranging from 35 to 70 mg/dL and 1.2 to 2.4 mg/dL, respectively.

At 2½ years of age, he experienced the onset of ataxia and minor motor seizures, and he lost the ability to walk independently. Examination showed growth retardation (weight < third percentile), microcephaly (occipitofrontal circumference < 3rd percentile), truncal titubation, diffuse hypotonia, and diminished deep tendon reflexes. His blood pressure (BP) was normal. Blood smear, CSF profile (protein, glucose, and cell count) and electromyogram (EMG) were normal. An EEG demonstrated high-voltage, diffuse, slow wave bursts, and a computerized tomographic (CT) scan showed mild cortical atrophy. His serum electrolyte values (sodium, chloride, potassium) were normal, and BUN and serum creatinine concentrations were only 30 mg/dL and 1.9 mg/dL, respectively (Table). Clonazepam therapy was started and the seizure frequency decreased.

At 3½ years of age, he had his first grand mal seizure. His BP remained normal, and BUN and creatinine concentrations were 37 mg/dL and 1.9 mg/dL, respectively. Phenytoin sodium was added to the anticonvulsant regimen.

At 4 years of age, he was rehospitalized because of poor seizure control. Examination continued to show hypotonia, truncal ataxia, hyporeflexia, and inability to walk unaided. The BUN and creatinine concentrations were 35 mg/dL and 2.1 mg/dL, respectively. Results of the following laboratory investigations were normal or negative: serum amino acid chromatography, serum copper and ceruloplasmin evaluation, urine arylsulfatase concentration, serum ammonia level, urine homovanillic acid (HVA) and vanillylmandelic acid (VMA) excretion, and CSF examination including IgG-albumin ratio and oligoclonal IgG. Needle EMG and nerve conduction velocities were normal. An EEG showed a slow, dominant rhythm and high-voltage epileptiform discharges. A CT scan continued to show mild, diffuse cerebral atrophy. The anticonvulsant regimen was changed to valproic acid and phenobarbital, which resulted in better control of seizures.

Case 2.—This boy was the full-term product of an uncomplicated pregnancy and delivery. At 3 days of age, the diagnosis of

Renal Function and Metabolic Parameters at the Onset of Neurologic Signs and Symptoms*

Case	BUN, mg/dL	Creatinine, mg/dL	Calcium, mg/dL	Phosphorus, mg/dL	CO_2 content, mEq/L
1					
Ataxia, minor motor seizures	30	1.9	11.2	6.1	16
Grand mal seizures	37	1.9	9.9	4.0	16
2					
Ataxia	64	2.1	10.5	6.4	14
Minor motor and grand mal seizures	78	2.5	7.9	7.5	...
3					
Ataxia	63	3.9	10.9	5.6	21
Minor motor seizures	62	3.3	10.6	4.2	24

*All three children had concomitant intellectual retardation.

posterior urethral valves and secondary reflux nephropathy was made. During the subsequent six months, he underwent several surgical procedures including valve resection, ureteral reimplantation, vesicostomy, and ultimately left nephrectomy. The BUN and serum creatinine concentrations ranged from 40 to 82 mg/dL and 1.1 to 3.1 mg/dL, respectively, during the first 2 years of life.

He sat at 10 months of age and crawled at 15 months. He acquired no recognizable words and never walked.

At 17 months of age, truncal instability appeared. Examination disclosed a small child (height and weight < the third percentile) whose head circumference was at the 50th percentile. He exhibited hypotonia, hyporeflexia, and truncal ataxia. His BP was normal. Laboratory evaluations disclosed the following values: serum electrolyte and serum magnesium, normal; BUN, 64 mg/dL; creatinine, 2.1 mg/dL; CT brain scan, normal; CSF profile, normal; and urine tests for HVA and VMA, negative. An EEG was abnormal with generalized rhythmic slowing. At 18 months of age, minor motor and grand mal seizures began. His renal function, BP, and serum electrolyte values were unchanged (Table). A repeated EEG was again abnormal, now with frequent epileptiform discharges. Phenobarbital and, later, phenytoin were prescribed. During the subsequent months, there was gradual deterioration until his death at 36 months of age. No autopsy was performed.

CASE 3.—This dizygotic twin was the 1,700-g product of an uncomplicated 34 weeks' gestation. The infant experienced mild, transient respiratory distress necessitating supplemental oxygen for 24 hours. However, he remained in the hospital for eight weeks because of poor growth and persistent azotemia (BUN, 50 mg/dL). The diagnosis of hypoplastic kidneys was made, and at 5 months of age, a ureterostomy was performed. He subsequently had frequent urinary tract infections.

He walked at 2 years of age and was slower than his twin sibling in all areas of psychomotor development. At 5½ years of age, he experienced the onset of minor motor seizures. An EEG was abnormal with frequent generalized 2 to 4/s spike-and-wave discharges. His BP was normal. Serum electrolyte and serum magnesium levels were normal. The BUN and serum creatinine concentrations were 62 mg/dL and 3.3 mg/dL, respectively (Table). Treatment with phenobarbital and ethosuximide was started; later, clonazepam was added to the regimen.

The azotemia increased, and at 6½ years of age, he was admitted to the hospital with nausea, vomiting, and a BUN concentration of 170 mg/dL. Because of his severe psychomotor retardation, long-term dialysis or transplantation was not started. Instead, a single peritoneal dialysis was performed, and a low-protein diet high in essential amino acids was started. During the subsequent year, his BUN concentration ranged between 39 and 62 mg/dL.

At 7½ years of age, he was hospitalized because of increasingly frequent seizures. Examination revealed a small child (weight, height, and head circumference all < the third percentile) who exhibited hypotonia, diffuse muscle wasting, truncal ataxia, and a wide-based gait. The BUN and serum creatinine concentrations were 63 mg/dL and 3.9 mg/dL, respectively. Results of the CSF profile, CT brain scan, urine tests for amino acids, tests for serum ammonia and CSF aluminum, needle EMG and nerve conduction velocity testing were normal. The EEG remained abnormal with diffuse, slow activity interspersed with diffuse 2.5 to 3/s spike-and-wave discharges.

During the subsequent six months, uremia became increasingly severe and the child died. No autopsy was performed.

COMMENT

Encephalopathy is a commonly recognized complication of azotemia and consists principally of alterations in mental function and involuntary motor phenomena such as tremor, asterixis, myoclonus, and convulsions.[1-3] Associated features may include cranial nerve abnormalities, cerebellar system dysfunction, and alterations in muscle tone and deep tendon reflexes.[4] Although encephalopathy may occur during acute renal failure, it is more often seen after chronic azotemia and, in adults, as a preterminal event when the glomerular filtration rate (GFR) is less than 10 mL/min.

Baluarte and co-workers[5] described a distinct neurologic syndrome characterized by myoclonus, dysarthria, seizures, dementia, coma, and an abnormal EEG in six children with chronic renal failure secondary to congenital renal disorders. The encephalopathy occurred between the ages of 26 months and 10 years, at a time when renal failure was far advanced (GFR, 5 to 10 mL/min/1.73 sq m).

Unlike the patients reported by Baluarte and co-workers, the encephalopathy in our patients began at a time when renal failure was only moderately advanced (GFR, 15 to 25 mL/min/1.73 sq m). Cerebellar signs and symptoms were prominent at the onset of the encephalopathy, and seizures (initially minor motor) began concurrently or shortly thereafter. All three children exhibited intellectual retardation.

The pathogenesis of uremic encephalopathy in these and other patients remains speculative. In general, the neuropathological findings are nonspecific and consist primarily of diffuse neuronal abnormalities and glial proliferation. However, necrosis of the granular cell layer of the cerebellar cortex is often found and may be related to the prominence of cerebellar signs and symptoms in these children.[6] Most authors attribute the encephalopathy to metabolic derangements, such as accumulation of neurotoxic organic acids and inhibition of cerebral enzyme systems by uremic

toxins.[7,8] Baluarte and co-workers[5] cited an additional mechanism, and they suggested that in their children, the encephalopathy may have been the result of aluminum intoxication. We measured the CSF aluminum concentration for patient 3, and we found it to be normal.

The variable response of the neurologic dysfunction to therapeutic measures makes it difficult to decide when or if to begin therapy. The decision is further complicated by the often poor correlation between neurologic symptoms and the degree of metabolic alteration.[9] In the experience of Baluarte et al,[5] dialysis and successful renal transplantation did not halt the progression of the encephalopathy. In contrast, other authors suggested that in adults, early aggressive dialysis and/or transplantation may improve the neurologic status of most patients.[10] This is particularly true for uremic polyneuropathy.[11,12]

Our experience suggests that the developing nervous system of the infant and young child may be particularly sensitive to the effects of chronic azotemia. Each of our patients exhibited diffuse CNS dysfunction with seizures and intellectual and motor retardation. Despite the fact that the neurologic abnormalities began when the renal failure was only moderately advanced, it is tempting to recommend that such young children with CNS signs and symptoms receive dialysis or transplantation early. Although data to support this recommendation are lacking, such an approach should be considered in an attempt to alter the progression of the serious nervous system dysfunction.

Nonproprietary Names and Trademarks of Drugs

Clonazepam—*Clonopin.*
Ethosuximide—*Zarontin.*
Valproic acid—*Depakene.*

References

1. Tyler HR: Neurologic disorders in renal failure. *Am J Med* 44:734-748, 1968.
2. Raskin NH, Fishman RA: Neurologic disorders in renal failure. *N Engl J Med* 294:143-148, 204-210, 1976.
3. Nissenson AR, Levin ML, Klawans HL, et al: Neurological sequelae of end stage renal disease. *J Chron Dis* 30:705-733, 1976.
4. Cullen RF: Neurologic complication of chronic renal disease, in Strauss J (ed): *Pediatric Nephrology.* New York, Stratton Intercontinental Medical Book Corp, 1976, pp 453-463.
5. Baluarte HJ, Gruskin AB, Hiner L, et al: Encephalopathy in children with chronic renal failure, abstracted. *Pediatr Res* 11:547, 1977.
6. Olsen S: The brain in uremia. *Acta Psychiatr Neurol Scand* 36:1-122, 1961.
7. Fishman RA, Raskin NH: Experimental uremic encephalopathy: Permeability ion exchange and brain spaces. *Trans Am Neurol Assoc* 90:71-75, 1965.
8. Hicks JM, Young DS, Wootton IDP: The effect of uremic blood constituents on certain cerebral enzymes. *Clin Chim Acta* 9:228-235, 1964.
9. Glaser GH: Brain dysfunction in uremia. *Res Publ Assoc Res Nerv Ment Dis* 53:173-199, 1974.
10. Dianapoli RP, Johnson WJ, Lambert EH: Experience with a combined hemodialysis-renal transplantation program: Neurologic aspects. *Mayo Clin Proc* 41:809-820, 1966.
11. Jebsen RH, Tenckhoff H, Honet JC: Natural history of uremic polyneuropathy and effects of dialysis. *N Engl J Med* 277:237-333, 1967.
12. Bolton CF, Baltzan MA, Baltzan RB: Effects of renal transplantation on uremic nephropathy. *N Engl J Med* 284:1170-1175, 1971.

A Lesson in Nutrition

During my early years at The Rockefeller Institute for Medical Research, I had the opportunity of knowing rather well two famous physicians whose nutritional habits symbolize the possibility of adapting successfully to extremely different dietary regimens. One was William Henry Welch (1850-1934), who was the architect of medical and public health sciences in America. The other was Oswald T. Avery (1877-1955), in whose laboratory I worked for 13 years and with whom I remained in close contact to the end of his life. Welch and Avery were approximately of the same height, had received similar college and medical educations, spent most of their lives in academic medicine, remained bachelors, smoked a great deal, took practically no physical exercise, and never tired of talking. But they differed completely in nutritional behavior.

Welch had a gargantuan appetite, with a preference for rich, well-seasoned foods. He was inordinately fond of sweets and was prone to end his meal with several helpings of ice cream—in a period when this meant real cream. He loved wine and hard liquor and seemed proud of the fact that his most violent form of exercise was taking off his shoes at night and putting them on in the morning. He early became obese but remained intellectually active to the end of his life. He died of cancer in his 85th year.

Avery ate sparingly. Two slices of toast, a few leaves of lettuce and several cups of coffee seemed to be his ideal meal. We used to say that he could be in nutritional balance only by fixing atmospheric nitrogen. He never weighed more than 90 pounds during the 30 years I knew him yet he was constantly active either in laboratory work or participating in discussions.... He died of cancer in his 79th year.

RENE DUBOS (*Am J Clin Nutr* 32:2623-2624, 1979).

Outcome of Hepatitis in Children With Acute Leukemia

William Malone, MD, Robert Novak, MD

• The cases of 31 children with acute leukemia and concurrent hepatitis were evaluated for the outcome of their hepatitis. Thirteen of these children had hepatitis B and 18 children had a non-B hepatitis. Chronic hepatitis developed in more than half of the children with acute hepatitis, with the majority of cases being of the chronic, active type. A majority of these children had received at least one blood transfusion in the preceding year. No relationship was seen between the development of chronicity of the liver disease and the management of the acute hepatitis or the state of underlying disease. With the potential for a cure for acute leukemia increasing, a method of reducing the sequelae of hepatitis in children with leukemia is needed.

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Hepatitis is recognized as a threat to children with cancer because they frequently receive blood-replacement therapy during intensive myelosuppressive therapy. Estimates of the risks of acquiring hepatitis B range from 1% to 20% among children with leukemia.[1-3] Recently, two patients cared for at St Jude Children's Research Hospital, Memphis, who had apparently been cured of leukemia later died of hepatitis and its complications. This led us to review our experience with hepatitis in children with acute leukemia.

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REPORT OF CASES

Case 1.—This 20-year-old man was diagnosed as having acute lymphocytic leukemia five years before his death. He was treated according to the "Total Therapy VIII" protocol (first with prednisone, vincristine sulfate and daunorubicin hydrochloride, followed by cranial irradiation and intrathecal methotrexate sodium for CNS prophylaxis, and then maintenance therapy with mercaptopurine, methotrexate and cyclophosphamide)[4] and remained in continuous, complete remission.

One month before this therapy was to be completed, nausea and vomiting developed. On physical examination, he had a low-grade fever and mild scleral icterus. Laboratory evaluation showed an SGOT level of 72 Karmen units (normal level, 6 to 40 units) and his serum contained the hepatitis B surface antigen (HB_sAg). A diagnosis of acute hepatitis B was made. The hepatitis B antigenemia and elevation in transaminase levels persisted for the next 21 months. With the development of marked jaundice in September 1977, a percutaneous liver biopsy was performed; the specimen showed chronic active hepatitis with cirrhosis. Over the next six months, the patient's condition progressively deteriorated despite prednisone therapy, salt restriction, and the administration of diuretics. No autopsy was obtained.

Case 2.—This 19-year-old man was first diagnosed as having acute lymphocytic leukemia 15 years before his death. He was treated according to the Total Therapy III protocol (prednisone and vincristine followed by craniospinal irradiation for CNS prophylaxis and then treatment with mercaptopurine, methotrexate, and cyclophosphamide for maintenance)[5] for three years, at which time his therapy was stopped. He remained in continuous, complete remission. Hepatomegaly and elevated SGOT levels were noted two months after completion of his therapy for leukemia. These abnormalities persisted for 18 months, and a liver biopsy specimen revealed "active portal fibrosis." Review of this biopsy specimen at a later date supported a diagnosis of chronic active hepatitis. A serum sample that had been kept frozen from the time of this biopsy was positive for the HB_sAg.

Hepatomegaly and abnormal transaminase levels persisted for the next four years, at which point he was lost to follow-up for four years. In September 1978, he returned and had obvious hepatic failure: the serum test for HB_sAg was still positive

and liver biopsy specimens showed chronic, active hepatitis with cirrhosis and hepatocellular carcinoma. Treatment with prednisone, diuretics, and salt restriction failed to halt the progressive hepatic failure. At autopsy, the liver showed chronic active hepatitis, advanced cirrhosis, and a massive hepatocellular carcinoma (Fig 1).

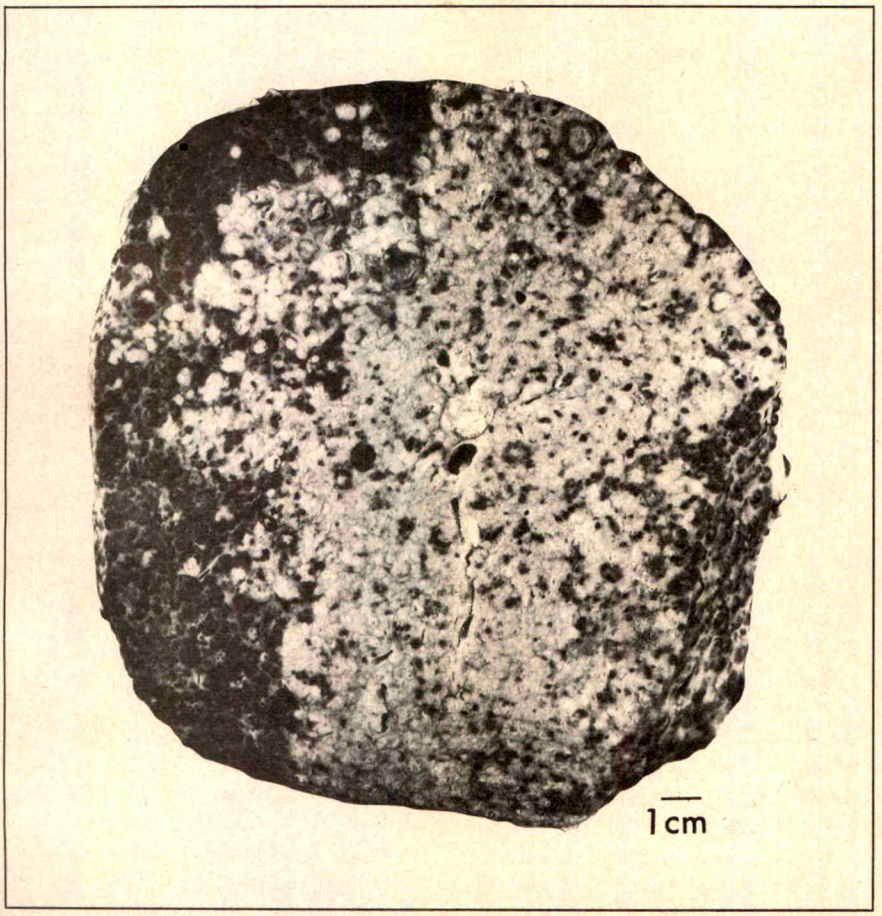

Fig 1.—Cross section through left lobe of liver shows extensive macronodular cirrhosis and massive amount of tumor.

PATIENTS AND METHODS

The medical records of all children with acute leukemia were reviewed for a concurrent diagnosis of hepatitis. Only those children who had had an HB_sAg determination and had isolated hepatitis that was not associated with a generalized infection were included. Chronic hepatitis was defined as the persistence of elevations of serum transaminase levels of 1.5 times the upper limit of normal for more than six months. The clinical record of each patient was reviewed to determine the type and status of the child's leukemia, the relation of the onset of hepatitis to blood transfusion, the management of the acute episode, and the subsequent course and outcome of the hepatitis. The HB_sAg status was determined by hemagglutination assay from 1970 to 1974 and by radioimmunoassay after 1974. Blood for transfusion was from volunteer donors and was screened by the method for determining HB_sAg that was in use at that time. Liver tissue obtained from biopsy or autopsy on any patient in this group was reviewed by two pathologists (who had no knowledge of the clinical data) and was classified according to standard criteria[6,7] as showing either no hepatitis, chronic persistent hepatitis, or chronic active hepatitis.

RESULTS

A total of 31 of the 797 children with acute leukemia had an episode of acute hepatitis as determined by the criteria just stated. Some form of chronic hepatitis developed in 18 patients (Fig 2).

There were 13 patients with HB_sAg-positive hepatitis. Eleven of these cases occurred before 1974. Four of these children had complete resolution of their hepatitis in less than six months and no longer carried HB_sAg. Two children had normal serum transaminase levels but were persistent carriers of HB_sAg. Of the seven patients with chronic hepatitis, six had hepatic tissue examined. Chronic

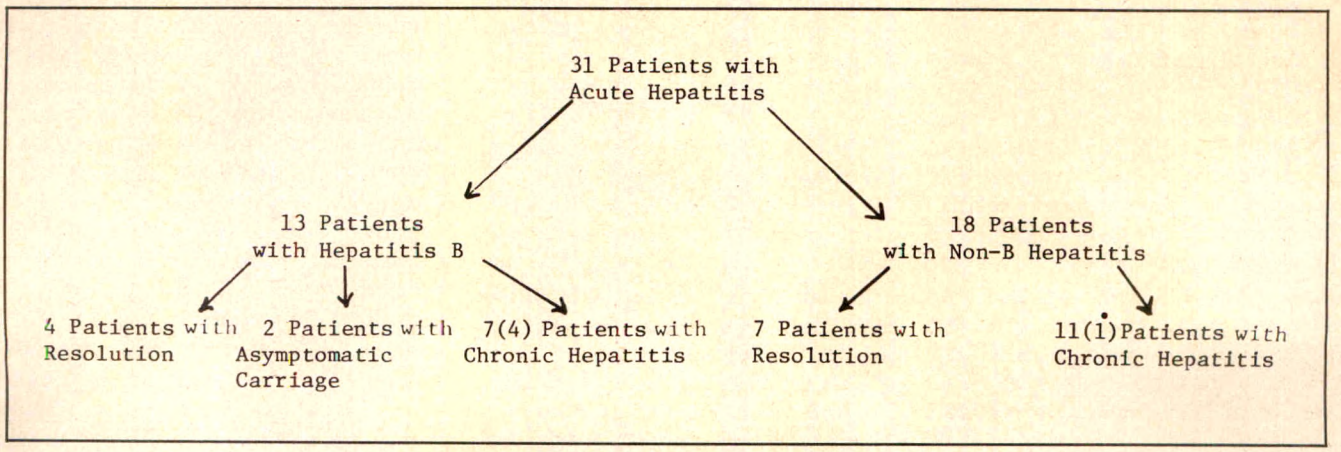

Fig 2.—Outcomes of 31 cases of acute hepatitis in children with leukemia. Numbers in parentheses are numbers of children who died of liver disease.

persistent hepatitis was found in two cases, and chronic active hepatitis with some degree of associated cirrhosis was present in four cases.

Acute lymphocytic leukemia was the basic disease in ten patients and acute nonlymphocytic leukemia was the basic disease in three cases; ten were in remission and three were in relapse of their leukemia. The type and status of the leukemia bore no relation to outcome. All patients had received two or more blood transfusions in the preceding 12 months. Three patients either had completed therapy or had chemotherapy discontinued at the time their hepatitis was diagnosed. All three had chronic hepatitis develop. In eight patients chemotherapy was withheld during the acute phase of the hepatitis (two to four weeks) and then it was resumed; four of these patients showed complete resolution, one became an asymptomatic HB_sAg carrier, and chronic hepatitis developed in three. Two patients had no interruption of therapy, one became a chronic asymptomatic carrier of HB_sAg, and chronic hepatitis developed in one.

Eighteen children had episodes of HB_sAg-negative hepatitis; ten of these cases occurred before 1974. Apparent complete resolution, with a return of serum transaminase levels to normal within six months, occurred in seven children. Chronic hepatitis developed in 11 children. Tissue examinations have been performed in eight of these patients, chronic persistent hepatitis was present in two cases and chronic active hepatitis in six cases.

The underlying disorder was acute lymphocytic leukemia in 16 patients and acute nonlymphocytic leukemia in two patients. Sixteen patients were in remission, and two were in relapse of their leukemia. Again, the type or status of the leukemia bore no relation to the outcome of the hepatitis. Blood transfusions had been administered to 16 of 18 patients in the previous year. The two patients who had not received a transfusion had brief illnesses with complete resolution, which was suggestive of hepatitis A. Two patients had their chemotherapy discontinued when hepatitis occurred; one had complete resolution of liver abnormalities and chronic hepatitis developed in one. Chemotherapy was withheld during the acute phase of hepatitis (two to six weeks) in 14 patients; chronic hepatitis developed in nine of these patients and five had complete resolution. Therapy was not interrupted in two cases; one patient's condition completely returned to normal, while chronic hepatitis developed in the other.

COMMENT

Chronic hepatitis developed in 18 of 31 patients with acute leukemia who had an episode of acute hepatitis. The development of hepatitis is an acknowledged risk in children who require multiple infusions of blood and blood products.[8,9] Twenty-nine of the 31 patients and all 18 patients in whom hepatitis developed had received transfusions in the preceding six months. The relative decrease in the frequency of HB_sAg-positive cases after the introduction of sensative HB_sAg screening methods and the steady frequency of the HB_sAg-negative cases is consistent with what has been observed in previous series of cases of posttransfusion hepatitis.[8,9]

Analysis of hepatitis cases is complicated in patients with cancer because they often receive potentially hepatotoxic agents during therapy.[10,11] The characteristic histologic changes seen in the liver biopsy specimens, the association of the HB_sAg in some cases, and the lack of effect on the course of the hepatic dysfunction from alterations in drug therapy suggest that our cases were not drug related.

Hepatitis Carriers

In the general population, Perman and Grand reported that there is a 10% risk of becoming a carrier of HB_sAg after becoming HB_s Ag-positive.[12] Of these long-term carriers, approximately 60% will have chronic persistent hepatitis develop and 10% will have chronic active hepatitis develop.[13] In our patients with acute leukemia and hepatitis B, nine of 13 (69%) became long-term HB_sAg carriers, at least three of nine (33%) of these long-term carriers had chronic persistent hepatitis, and four of nine (44%) had chronic active hepatitis. This represents a greater frequency of chronicity along with a disturbing increase in the incidence of an aggressive, potentially fatal form of the disease.

In our patients with non-B hepatitis, evidence of chronic hepatitis developed in 11 of 18 patients and at least six had chronic active hepatitis confirmed by analysis of liver biopsy specimens. Studies of non-A, non-B posttransfusion hepatitis in patients undergoing open heart surgery[14,15] have shown an incidence of progression to chronic hepatitis of approximately 40%, with from 23% to 35% having chronic active hepatitis confirmed by analysis of biopsy specimens. This suggests that the course of non-A, non-B hepatitis may not be much worse in our patients with cancer than in the normal host. It also offers the hope that prophylactic regimens that are effective in patients who do not have leukemia might be effective with leukemia.

Possible Beneficial Effects of Hepatitis

Barton and Conrad[16] have suggested that hepatitis in patients with acute myelogenous leukemia may have a beneficial effect on the patients' outcome. Our series is too heterogeneous and our long-term follow-up is too limited to rigorously support or deny this assertion. It is important to remember the limitations of the data presented by these authors, namely that no clear distinction between posttransfusion hepatic dysfunction and drug-induced hepatic dysfunction is made and that no histologic proof of hepatitis is given. Based on the patients in our series, our belief is that the occurrence of hepatitis in a patient with acute leukemia is undesirable. Not only is there a risk of chronic liver disease, but hepatic dysfunction may limit the amount of effective chemotherapy that can be administered at a crucial point in therapy.

Implications for Therapy

As chemotherapy becomes more effective and estimates of a 40% cure

rate[17] in childhood null-cell acute lymphocytic leukemia are made, concern for long-term sequelae and complications of therapy have become more important. The role and value of steroid therapy in chronic active hepatitis is controversial,[18] and no studies have been performed in the population with childhood leukemia. Our data offer no suggestion as to the appropriate management and modification of the potentially immunosuppressive and hepatotoxic chemotherapy these patients require for control of leukemia. Advances in blood-banking techniques have decreased the incidence of hepatitis, especially of HB_sAg-positive hepatitis, after transfusion but will probably not eliminate it.[10] The use of prophylactic γ-globulin administration with transfusion has been shown to be of value in preventing chronic non-A, non-B hepatitis in a small number of patients[15] and deserves a trial in the patient with childhood cancer. To aid in the development of methods of management and of measures to prevent this complication, we must define the problem of hepatitis in childhood leukemia more precisely with firm data from liver biopsy specimens.

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Nonproprietary Names and Trademarks of Drugs

Daunorubicin hydrochloride—*Cerubidine.*
Vincristine sulfate—*Oncovin.*

References

1. Blumberg BS, Alter HJ, Visnick S, et al: A new antigen in leukemic sera. *JAMA* 191:541-546, 1965.
2. Wands JR, Chura CM, Roll FJ, et al: Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* 68:105-112, 1975.
3. Tabor E, Gerety RJ, Mott M, et al: Prevalence of hepatitis B in a high-risk setting: A serologic study of patients and staff in pediatric oncology unit. *Pediatrics* 61:711-715, 1978.
4. Aur RJ, Simone JV, Verzosa MS, et al: Childhood leukemia: Study VIII. *Cancer* 42:2123-2134, 1978.
5. George P, Hernandez K, Hustu O, et al: A study of "total therapy" of acute lymphocytic leukemia in children. *J Pediatr* 72:399-408, 1968.
6. Morphological criteria in viral hepatitis. *Lancet* 1:333-337, 1971.
7. Ludwig J: A review of lobular, portal, and periportal hepatitis. *Hum Pathol* 8:869-876, 1977.
8. Conrad ME: Current status of posttransfusion hepatitis. *Am J Hematol* 1:357-365, 1976.
9. Lesesne HR, Morgan JE, Blatt PM, et al: Liver biopsy in hemophilia A. *Ann Intern Med* 86:703-707, 1977.
10. Einhorn M, Davidsohn I: Hepatotoxicity of mercaptopurine. *JAMA* 188:802-806, 1964.
11. McIntosh S, Davidson DL, O'Brien RT, et al: Methotrexate hepatotoxicity in children with leukemia. *J Pediatr* 90:1019-1021, 1977.
12. Perman JA, Grand RJ: Acute and chronic hepatitis in children. *Postgrad Med J* 63:191-200, 1978.
13. Mihas AA, Conrad ME: Hepatitis B antigen and the liver. *Medicine* 57:129-150, 1978.
14. Berman M, Alter HJ, Ishak KG, et al: The chronic sequelae of non-A, non-B hepatitis. *Ann Intern Med* 91:1-6, 1979.
15. Knodell RG, Conrad ME, Ishak KG: Development of chronic liver disease after acute non-A, non-B posttransfusion hepatitis: Role of γ-globulin prophylaxis in its prevention. *Gastroenterology* 72:902-909, 1977.
16. Barton JC, Conrad ME: Beneficial effects of hepatitis in patients with acute myelogenous leukemia. *Ann Intern Med* 90:188-190, 1979.
17. George SL, Aur RJA, Mauer AM, et al: A reappraisal of the results of stopping therapy in childhood leukemia. *N Engl J Med* 300:269-273, 1979.
18. Harris RC, Tabar E: When is hepatitis chronic? *J Pediatr* 95:551-552, 1979.

Multicystic Ovaries Detected by Sonography

Alan N. Lindsay, MD; Mary L. Voorhess, MD; Margaret H. MacGillivray, MD

• **Four girls with long-standing primary hypothyroidism, three of whom had modest sexual precocity, were found to have multicystic ovaries when evaluated by pelvic sonography. The ovarian lesions were not evident clinically in three of the patients. The cysts regressed rapidly with thyroid replacement. The use of pelvic sonography may show that multicystic ovaries occur more frequently in profoundly hypothyroid girls than has been reported previously. There was a marked discrepancy between baseline plasma luteinizing hormone (LH) levels, which were elevated in three of four girls, and the urinary LH output, which was low or normal. Plasma and urinary follicle-stimulating hormone levels were normal. Two of three girls tested with luteinizing hormone-releasing hormone infusion had attenuated gonadotropin responses, while the third reacted normally. Our hormonal data do not provide an explanation for the cystic ovarian changes and early sexual development.**

(*Am J Dis Child* 134:588-592, 1980)

It is known that precocious sexual development occurs in some children with severe and long-standing primary hypothyroidism,[1-6] but multicystic ovaries have been reported in only a small group of affected girls.[2-11] We describe four hypothyroid patients with multicystic ovaries detected by pelvic sonography, a technique not mentioned in previously reported cases. The experience with our patients suggests that pelvic sonography is a useful noninvasive method both for initial diagnosis of multicystic ovaries and for demonstrating the rapid regression of cysts with thyroid replacement. We also report results of our evaluation of plasma and urinary gonadotropins before and after thyroid treatment and during luteinizing hormone-releasing hormone (LHRH) stimulation and discuss the possible mechanisms responsible for the development of sexual precocity and multicystic ovaries in hypothyroid girls.

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METHODS

Baseline serum levels of thyroxine (T_4) and thyroid-stimulating hormone (TSH) and plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and 24-hour urinary concentrations of LH and FSH were obtained before and at variable times after the start of thyroid replacement. Samples for plasma cortisol and serum prolactin were obtained at approximately 8 AM prior to treatment. Twenty-four-hour urine specimens for 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) were collected prior to thyroid treatment. Intravenous (IV) three-hour LHRH stimulation tests using 100 μg of LHRH were performed according to the method of Reiter et al[12] on three girls (patients 1 to 3). Plasma samples were obtained at 20-minute intervals before and during the LHRH stimulation. In addition, urine was collected for three-hour periods before, during, and after LHRH infusion for gonadotropin analyses. Patient 4 also underwent a thyrotropin-releasing hormone (TRH) stimulation test, during which she received an IV bolus injection of 200 μg of TRH. Concentrations of LH, FSH, and TSH were measured at 0, 30, 60, 90, 120, 150, and 180 minutes.

Plasma FSH and LH levels were measured by radioimmunoassay (RIA) with use of National Pituitary Agency (NPA) reference standard LER 907 and NPA antisera for LH and FSH. The interassay coefficient of variation for FSH and LH was 8.1 and 7.3, respectively. Urine FSH and LH levels were measured by RIA with use of the World Health Organization Human Menopausal Gonadotropin standard (second IRP-HMG). The T_4, TSH, cortisol, and prolactin concentrations were measured by RIA; 17-OHCS levels were measured by the Glenn-Nelson procedure and 17-KS levels were measured by the Zimmerman reaction. Written informed consents for the LHRH studies were obtained from the patients and/or parents.

Pelvic ultrasound was performed with a gray scale contact scanner. Bone ages were determined according to the standards of Greulich and Pyle.[13]

REPORT OF CASES

CASE 1.—A 12-year 4-month-old girl was found to be hypothyroid six years prior to admission, but received no treatment

in Children With Hypothyroidism

because she was unavailable for follow-up. Thelarche, pubarche, and menarche took place at age 11 years. Her menstrual cycles always were irregular, and she had menorrhagia for 13 days prior to hospitalization. Negligible linear growth had occurred during the preceding three years. Physical examination revealed Tanner stage 2 breasts and pubic hair development and hypertrophied labia minora. A left adnexal mass and adult-sized uterus were palpated on pelvic examination. Her height age was 10 years 3 months and bone age was 10 years. Skull x-ray films revealed an enlarged sella turcica, and pelvic sonography showed bilateral multicystic ovaries, the right measuring 7 × 5 × 4 cm and the left, 4.0 × 4.5 × 3.0 cm. After five weeks of thyroid replacement, the cysts had decreased in size dramatically. Menorrhagia ceased several days after the onset of thyroid treatment, and she has remained amenorrheic during the subsequent eight months.

Case 2.—A 12-year 3-month-old short, premenarcheal girl had experienced no linear growth during the previous two years. Thelarche and adrenarche had occurred at age 11 years. On physical examination, she had axillary sweat and early Tanner stage 2 breasts and pubic hair development. No abdominal masses were palpable. Her height age was 7 years 10 months and bone age was 10 years. Skull x-ray films were normal. On pelvic sonography, she was found to have bilateral multicystic ovaries. The right ovary measured 3 × 2 × 4 cm and the left, 3.5 × 3.5 × 2.0 cm. The largest cyst had a diameter of 2 cm. Repeated sonography after two months of thyroid therapy revealed almost complete resolution of the cysts.

Case 3.—A 16-year 2-month-old girl had grown only 2 cm since age 11. Although menarche occurred at 13 years, she only had six subsequent menstrual periods. She exhibited Tanner stage 2 breasts and pubic hair development. No abdominal masses were palpable. Her height age was 9 years 3 months. Bone age was 11 years, and skull x-ray films were normal. Pelvic sonography demonstrated bilateral multicystic ovaries, the right measuring 2 × 2 × 2 cm

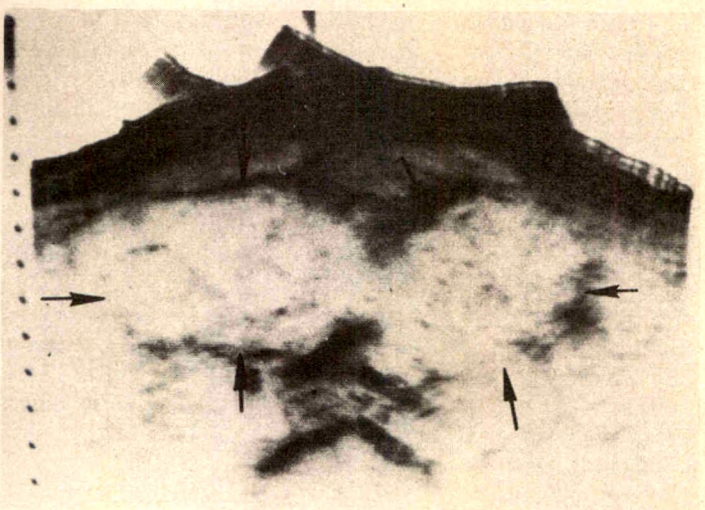

Fig 1.—Pelvic ultrasound of patient 4 prior to thyroid therapy. Arrows outline enlarged ovaries with multiple cysts.

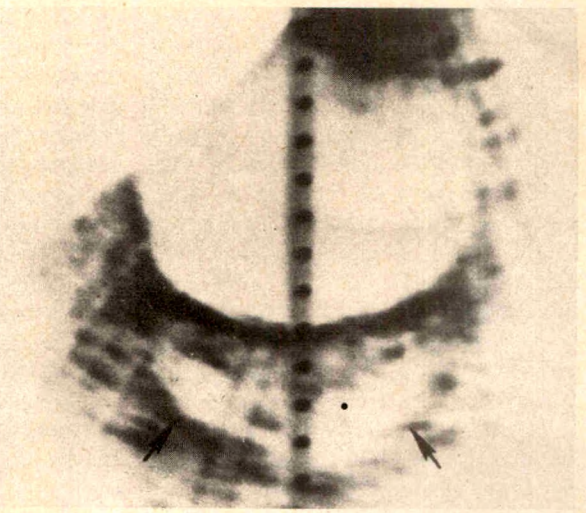

Fig 2.—Repeated pelvic ultrasound of patient 4 after three months of thyroid replacement. Arrows locate smaller ovaries with no cysts present.

and the left, 4.0 × 3.5 × 4.0 cm, with the largest cyst diameter 4 cm. The cysts completely resolved after one month and menses had not yet resumed after six months of thyroid therapy.

CASE 4.—A 14-year 5-month-old girl experienced dramatic deceleration in her linear growth rate at 10 years of age and growth cessation at age 13. Thelarche and adrenarche occurred at age 11 years and menarche occurred at age 14. Subsequent menstrual periods were irregular. Persistent, severe galactorrhea, which was occasionally blood-tinged, began at 14 years. She exhibited Tanner stage 3 breast development, Tanner stage 2 pubic hair, and hypertrophy of her labia minora. There were no palpable abdominal masses. Her height age was 11 years 1 month and bone age was 11 years. Skull x-ray films revealed an enlarged sella turcica, and a computerized tomography scan demonstrated an enlarged pituitary gland without ventricular dilation. Pelvic ultrasound disclosed bilateral multicystic ovaries (Fig 1) measuring 7.0 × 5.5 × 8.0 cm on the right and 4.0 × 5.0 × 5.5 cm on the left. After six months of thyroid therapy, she no longer had galactorrhea and had had no menses. A repeated sonogram after three months of therapy revealed near complete resolution of the ovarian cysts (Fig 2).

RESULTS

Baseline serum T_4, TSH, prolactin, plasma cortisol, plasma, urinary FSH and LH, and urinary 17-KS and 17-OHCS values, as well as post-treatment T_4, TSH, and gonadotropin values are given in Table 1. All four patients had very low serum T_4 and high TSH levels. Baseline plasma LH concentrations were increased in three patients and returned to the normal range following thyroid replacement. All plasma FSH levels were within the normal range. Baseline 24-hour urinary LH and FSH concentrations were normal or low and increased with thyroid therapy. The output of urinary 17-KS and 17-OHCS was low for age. Serum prolactin concentrations were mildly to moderately elevated in three of four patients.

Table 2 summarizes the results of LHRH testing in three patients. Two patients (1 and 4) had no rise in serum or urine gonadotropin values with LHRH stimulation. The baseline plasma LH concentrations were high in patient 1 and normal in patient 4. Patient 3 had elevated baseline LH concentrations and showed a twofold to threefold response to LHRH.

Patient 4 also had a TRH stimulation test; plasma TSH increased from a baseline value of 1,000 μU/mL to a peak concentration of 2,000 μU/mL at 30 minutes. A slight increase in FSH (3.1 mIU/mL to 5.9 mIU/mL) and a minimal rise in LH (4.9 mIU/mL to 5.6 mIU/mL) were noted.

Patient	CA/BA	Time
1	12 yr 4 mo/ 10 yr	Before treatment
		3 mo after treatment
2	12 yr 3 mo/ 10 yr	Before treatment
		2 mo after treatment
3	16 yr 2 mo/ 11 yr	Before treatment
		4 mo after treatment
4	14 yr 5 mo/ 11 yr	Before treatment
		3 mo after treatment
Normal values		

COMMENT

Although sexual precocity is relatively common in children with hypothyroidism, multicystic ovaries have rarely been reported. First described by Silver in 1958,[7] there has been a total of 11 cases reported in the pediatric literature (Table 3). All were identified by discovery of a mass on abdominal or pelvic examination. Five girls had ovarian surgery; three underwent biopsies to rule out tumors,[2,3,7] and two underwent gonadectomy because of ovarian torsion.[8-11] The pathology reports noted cystic follicles with partial to excessive luteinization of the theca interna and generally decreased numbers of primordial follicles. The six other patients were treated conservatively with thyroid replacement, which led to resolution of the ovarian enlargement.

We are describing four additional girls with severe hypothyroidism who had multicystic ovaries confirmed by pelvic sonography. By abdominal examination, a definite mass was palpable in only one of the four. To our knowledge, patient 2 is the first case of a girl with multicystic ovaries and hypothyroidism diagnosed prior to menarche to be reported. With thyroid replacement, all of our patients showed rapid regression of their cysts within one to three months. Interestingly, these patients represent four consecutive cases of severe hypothyroidism referred to our endocrine clinic. Since multicystic ovaries were unsuspected in three of the four patients until discovered by pelvic sonography, this disorder may be much more common than was formerly believed.

The association of hypothyroidism and precocious puberty was first described by Kendle[1] in 1905, but it was not until half a century later that further cases were reported.[2,7,8] Up to 1972, only 23 cases had been recorded,[4] but since that time, it has become apparent that early sexual development is a more frequent occurrence in hypothyroid children than was thought previously. In a review of 54 cases of primary hypothyroidism, Barnes et al[5] found that 58% of the girls and 56% of the boys showed some degree of sexual precocity if sexual maturation was compared with bone age rather than chronologic age.

On the basis of osseous maturation, three of our patients can be considered precocious even though they began pubertal development at an appropriate chronologic age. Features described in the earlier reports were noted in our patients, ie, grossly irregular menses with relatively immature breast and pubic hair development, galactorrhea in one, and labia minora hypertrophy in two. Following thyroxine supplementation, all three had a cessation of menses. The fourth patient, patient 2, could not be considered precocious because her secondary sexual development was appropriate for her bone age. Nevertheless, she had hormonal and ovarian findings that were similar to those of the other three patients.

For the most part, our hormonal results are similar to those previously recorded in children with primary hypothyroidism and sexual precocity.

Table 1.—Plasma and Urinary Values Prior to and After Thyroid Replacement*

T_4, μg/dL	TSH, μU/mL	Plasma LH, MIU/mL	Plasma FSH, MIU/mL	Urine LH, IU/24 hr	Urine FSH, IU/24 hr	Prolactin, ng/mL	Plasma Cortisol, μg/dL	Urine 17-KS, mg/24 hr	Urine 17-OHCS mg/sq m/24 hr
0	607	11.1	5.8	7.3	6.2	60	13	0.3	1.7
8.8	3.4	2.2	< 1.2	8.9	2.3				
0.3	840	13.1	2.0	0.5	0.8	46.8			
9.1	< 3.1	< 1.2	4.3	6.3	1.7				
0	510	11.5	3.1	5.7	6.9	34.6	20.5	0.5	1.2
11.6	4.4	3.8	4.6	14.2	8.3				
0.4	400	5.0	4.9	12.8	4.0	27.3	7.0	3.2	1.9
7.3	3.1	2.3	6.8	13.8	6.9				
5-13	3-15	2-8	< 8	4-16	3-11	6-30	10-25	4-13	2-4

*CA indicates chronologic age, BA, bone age; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; 17-KS, 17-ketosteroids; 17-OHCS, 17-hydroxycortico steroids.

Table 2.—Results of Three-Hour LHRH Infusion Test*

	Plasma†				Urinary					
	LH (mIU/mL)		FSH (mIU/mL)		LH (IU/3 hr)			FSH (IU/3 hr)		
Patient	Basal	Peak	Basal	Peak	Preinfusion	Infusion	Postinfusion	Preinfusion	Infusion	Postinfusion
1	10.5	11.4	5.4	5.8	1.7	1.6	1.0	1.0	0.6	0.6
2	9.4	22.6	3.3	4.6	0.4	4.2	2.3	0.2	0.7	0.6
3	4.8	4.7	4.0	5.2	0.9	0.7	1.0	0.7	0.5	0.7

*LHRH indicates luteinizing hormone-releasing hormone.
†LH indicates luteinizing hormone; FSH, follicle-stimulating hormone.

Table 3.—Summary of Previously Reported Cases of Ovarian Enlargement in Girls With Hypothyroidism

Reference	Age, yr	Bone Age, yr	Breasts*	Pubic Hair*	Menses	Galactorrhea	Ovaries, cm	Sella Turcica Enlargement	PBI, μg/dL†
7	7.8	...	2	1	+	–	5 × 5, 5 × 5	–	BEI‡
2	8.7	6.0	2-3	2	+	+	6	+	0.8
2	7.1	5.8	3	1	+	+	3 × 3, 2 × 2	+	2.4
8	11.8	6.8	2	1	+	–	...	+	1.4
3	10.0	6.8	2	1	+	–	6 × 6	–	1.9
9	6.5	2.0	2	1	+	–	...	...	...
10	8.0	...	3	2	+	–	11 × 7	...	1.7
11	10.0	1.5	2	1	+	+	Adult	–	...
4	8.8	4.5	3	1	+	+	8 × 9	–	BEI§
5	12.6	10.0	3	2	+	–	15, 10	...	1.8
6	3.0	0.8	2	2	+	+	9 × 5, 1 × 3	...	T_4‖

*Tanner stage estimated from description of patient.
†Normal values = 4 to 8 μg/dL.
‡BEI (butanol-extractable iodine) = 0.5 μg/dL.
§BEI = 0.3 μg/dL (normal, 4.5 to 7.5 μg/dL).
‖T_4 = 2.8 μg/dL (normal, 4 to 12 μg/dL).

All have had profound hypothyroidism with high TSH levels. Prolactin concentrations were measured in five previously described patients,[4,6] and all had markedly elevated levels in contrast to the modest increases seen in three of our four subjects. Plasma gonadotropins have been measured in 23 cases.[4-6,14-16] In one series,[15] both LH and FSH levels were increased, with a predominance of FSH. Others[4,6,16] reported higher LH than FSH concentrations. Three of our patients had high plasma LH levels, but the FSH concentration was normal in each.

It is possible that the ovarian cysts seen in hypothyroid girls result from chronic LH stimulation since an association between high LH concentration and cyst formation has been reported. McNatty et al[17] found that cysts occurred in many women whose follicular fluid had increased amounts of LH. Furthermore, elevated LH in the presence of normal FSH has been implicated in the etiology of polycystic ovary disease.[18]

There have been several mechanisms proposed to explain the abnormal sexual maturation in girls with hypothyroidism: (1) an overlap in the pituitary hormonal feedback mechanism resulting in nonspecific hormone release in response to a single target gland deficiency[2]; (2) early maturation of the hypothalamic-pituitary-gonadal axis, such as occurs in idiopathic isosexual precocity; (3) decreased hepatic metabolism of sex steroids, producing a mild elevation of estrogen concentration[3]; (4) enhanced ovarian sensitivity to gonadotropins, as has been suggested from studies in hypothyroid rats[19]; (5) hyperprolactinemia, causing either increased estrogen production or gonadotropin secretion.[4-6] The diversity of proposals indicates the uncertain pathophysiologic features. Exceptions can be raised for each hypothesis.

We noted a discrepancy between baseline serum and urinary gonadotropin levels in our patients. Three of the four girls had elevated basal serum LH values but low to normal concentrations in their urine. In earlier case reports, urinary gonadotropin levels measured by bioassay were not elevated despite the presence of sexual precocity.[2-4,7,11,14,20,21] These results suggest an abnormality in either clearance or metabolism. Since steroids in hypothyroid subjects are known to have prolonged half-lives because of reduced metabolism and clearance,[22] it is possible that these processes, coupled with increased production, account for the elevated plasma LH levels in our patients. This explanation is strengthened by the observation that plasma LH levels fell in three of our four patients following thyroid replacement, and urinary values increased in all, albeit only slightly in two.

Attenuated pituitary responses to LHRH stimulation were seen in two of our three patients. Hemady et al[6] reported similar findings in two hypothyroid patients and attributed the abnormality to tonic stimulation that depleted the pituitary of readily releasable reserves of gonadotropins. It is noteworthy that both of our girls with poor responses to LHRH had enlarged sellas on skull x-ray film and that the girl with a normal response had a normal sella turcica. Hemady et al did not report skull x-ray film findings. It is possible that significant pituitary thyrotroph hyperplasia with physical compression of gonadotrophs occurs before there is diminished gonadotropin response to LHRH.

The precise mechanism that causes ovarian cyst formation and precocious sexual maturation in girls with severe long-standing hypothyroidism is not clear. The frequent occurrence of high plasma LH concentrations suggests that this hormone may have etiologic importance, but the role of the gonadotropins needs further clarification. Our experience indicates that abnormalities of the hypothalamic-pituitary-ovarian axis and multicystic ovaries may be more common than previously recognized. An accurate assessment of the frequency of cystic ovaries in primary hypothyroidism is now possible by use of pelvic ultrasound.

Since this article was submitted for publication, we have seen five additional girls with severe long-standing primary hypothyroidism. Two of the girls had multicystic ovaries detected by pelvic sonography, while the other three did not.

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Miriam Link assisted in the preparation of the manuscript and Oleta Denz and Barbara Babcock helped in the metabolic studies.

References

1. Kendle FW: Case of precocious puberty in a female cretin. *Br Med J* 1:246, 1905.

2. Van Wyk JJ, Grumbach MM: Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: An example of hormonal overlap in pituitary feedback. *J Pediatr* 57:416-435, 1960.

3. Wood LC, Olichney M, Locke H, et al: Syndrome of juvenile hypothyroidism associated with advanced sexual development. *J Clin Endocrinol Metab* 25:1289-1295, 1965.

4. Costin G, Kershnar AK, Kogut MD, et al: Prolactin activity in juvenile hypothyroidism and precocious puberty. *Pediatrics* 50:881-889, 1972.

5. Barnes ND, Hayles AB, Ryan RJ: Sexual maturation in juvenile hypothyroidism. *Mayo Clin Proc* 48:849-856, 1973.

6. Hemady ZS, Siler-Khodr TM, Najjar S: Precocious puberty in juvenile hypothyroidism. *J Pediatr* 92:55-59, 1978.

7. Silver HK: Juvenile hypothyroidism with precocious sexual development. *J Clin Endocrinol Metab* 18:886-891, 1958.

8. Van Gelderen HH: Precocious menstruation in hypothyroidism. *Arch Dis Child* 37:337-339, 1962.

9. Walczak M, Bartkowiak K, Bartkowiak Z: Vorzeitige Reifung (Pubertas praecox) bei einem 6½ jahrigen Madehen mit Hypothyreose. *Mschr Kinderheilk* 114:131-132, 1966.

10. Pabst HF, Pueschel S, Hillman DA: Etiologic interrelationship in Down's syndrome, hypothyroidism and precocious sexual development. *Pediatrics* 40:590-595, 1967.

11. Purohit KR, Bai YD: Precocious puberty with juvenile hypothyroidism. *Indian Paediatr* 5:330-332, 1968.

12. Reiter EO, Root AW, Duckett GE: LH and FSH levels in urine and serum of prepubertal and pubertal children receiving a three-hour infusion of LH-RH. *J Clin Endocrinol Metab* 44:56-61, 1977.

13. Greulich WW, Pyle SI: *Radiographic Atlas of Skeletal Development of the Hand and Wrist.* Stanford, Calif, Stanford University Press, 1955.

14. Laron Z, Karp M, Dolberg L: Juvenile hypothyroidism with testicular enlargement. *Acta Paediat Scand* 59:317-322, 1970.

15. Hopwood NJ, Lockhart LH, Bryan GT: Acquired hypothyroidism with muscular hypertrophy and precocious testicular enlargement. *J Pediatr* 85:233-236, 1974.

16. Lee PA, Blizzard RM: Serum gonadotropins in hypothyroid girls with and without sexual precocity. *Hopkins Med J* 135:55-60, 1974.

17. McNatty KP, Hunter WM, McNeilly AS, et al: Changes in the concentration of pituitary and steroid hormones in the follicular fluid of human Graafian follicles throughout the menstrual cycle. *J Endocrinol* 64:555-571, 1975.

18. Rebar R, Judd HL, Yen SSC, et al: Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *J Clin Invest* 57:1320-1329, 1976.

19. Mandl AM: Factors influencing ovarian sensitivity to gonadotropins. *J Endocrinol* 15:448-457, 1957.

20. Hayles AM, Hinrichs WL, Tauxe WN: Thyroid disease among children with Down's syndrome (mongolism). *Pediatrics* 36:608-614, 1965.

21. Jenkins ME: Precocious menstruation in hypothyroidism. *Am J Dis Child* 109:252-254, 1965.

22. Hellman L, Bradlow HL, Zumoff B: Recent advances in human steroid metabolism. *Adv Clin Chem* 13:1-35, 1970.

Small-Intestine Length in Infants and Children

Joseph R. Siebert, MS

• Small-intestine length from ligament of Treitz to ileocecal valve was measured in 183 infants and children ranging up to 15 years of age. Elongation of the intestine was rapid until crown-heel length was 60 cm and remained constant from 100 to 140 cm of body length. When patients were placed into three general diagnostic categories (congenital heart disease, abdominal lesions, and miscellaneous) no significant differences were found. However, several striking instances of abnormally long or short small intestines were encountered.

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The importance of the length of the small intestine has been recognized by surgeons preparing for resections,[1-7] by radiologists trying to pinpoint lesions in the intestinal tract,[8] and by pathologists desiring to assess the functional status of the digestive system at autopsy.[3,7] However, comprehensive studies of intestinal length in children, and for that matter adults, are relatively scarce.

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Such investigations, using different approaches, have produced variable data.[1,5,6,8-12] Some reports have given arbitrary statements of normal intestinal lengths while omitting the method by which such data were obtained.[1,2,5]

The most comprehensive portmortem study published to date[8] expressed intestinal length as a ratio of body length. Patient age or weight did not correlate with intestinal length. An association between abnormally long small intestines and congenital heart disease was suggested. In that study, the method of measuring the small intestine was not specified, and it was not stated whether the duodenum was included in the measurements.

The present study was based on a simple method for measuring length of the jejunum and ileum, avoiding stretch artifact. The relationship between small-intestine length and congenital heart disease was investigated, as was the possible effect of other diseases on small-intestine length.

METHODS

Data were collected from an autopsy population of 183 cases from 1972 to 1974. Ages ranged from prematurity (30 weeks' gestation) to 15 years.

At autopsy, the abdominal cavity was gently investigated. A ligature was placed around the small intestine at the duodenal-jejunal suspensory ligament (of Treitz) to mark the beginning of the jejunum. In infants and small children, all thoracoabdominal organs were kept intact during en bloc evisceration. In larger children, the gut was removed after ligating and dividing the jejunum at the ligament of Treitz, and the small bowel was removed by cutting across the mesenteric root from cecum to duodenum. Either method left the mesentery intact with jejunum and ileum, ensuring that the small intestine was not stretched.

After evisceration, most of the mesentery was removed by cutting it along the terminal arcade of the mesenteric vasculature. By leaving this portion of mesentery intact with the small intestine, stretching of the gut was prevented. Agonal intussusceptions were reduced before the bowel was measured. A 3-m length of No. 00 silk suture material previously knotted at 1-m intervals was clamped to the antimesenteric border of the jejunum at the ligament marking the ligament of Treitz. With two forceps, the suture was carefully laid along the small bowel to the ileocecal junction, and the length of the suture was then measured.

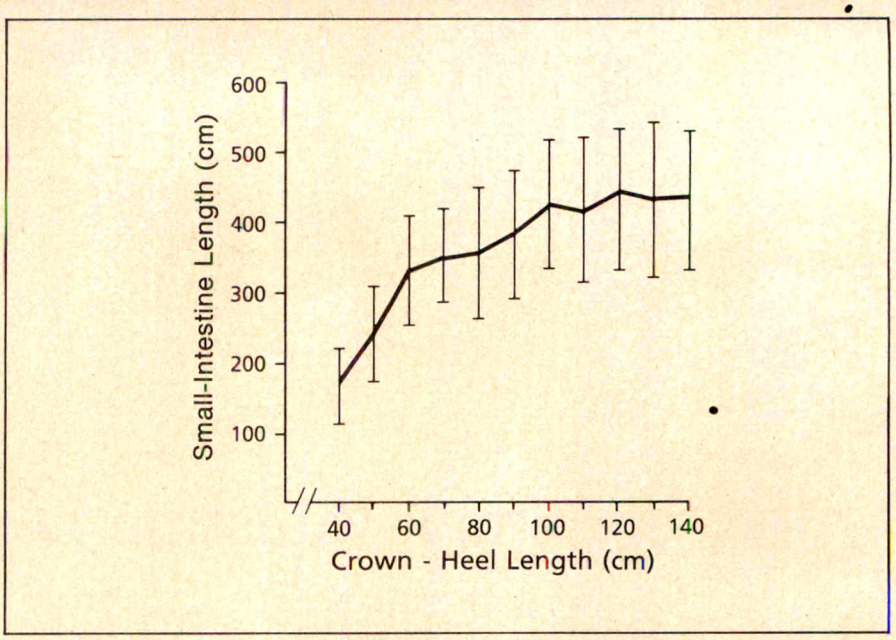
In at least one previous study, patients' ages and body weights did not correlate with small-intestine lengths.[8] The decision to study only the relationship of crown-heel

and small-intestine lengths was therefore made.

The cases were placed into 11 groups, in increments of 10-cm of the crown-heel length (Figure). Mean and SD of small-intestine lengths were calculated for each group. The cases were then placed into one of three diagnostic categories, congenital heart disease, intra-abdominal lesions, or "other." A one-way analysis of variance was performed between and among the categories.[13] The intra-abdominal lesions were itemized, and the mean of small-intestine lengths was calculated for each specific type of lesion.

RESULTS

The data are provided in the Figure and the Table. The Figure graphically details the means and SDs of all cases in the study. Considerable variation within each body-length category is apparent. The data approximate a curve, with the rate of small-intestine elongation decreasing noticeably when the body length reaches 60 cm, the length becoming essentially constant when the body length reaches 100 cm. A one-way analysis of variance of small-intestine lengths in the three categories of congenital heart disease, intra-abdominal lesions, and "others" showed no significant statistical differences within each body-length group. The Table itemizes the small-intestine lengths found in association with intra-abdominal lesions.



Small-intestine length vs crown-heel length, showing means and SDs.

Intra-abdominal Lesions and Small-Intestine Length

Lesion	n	Mean Crown-Heel Length, cm	Mean Small-Intestine Length, cm	Normal Small-Intestine Length, cm*
Atresia of colon	1	35	130	164 ± 54
Necrotizing enterocolitis	4	42	199	164 ± 54
Imperforate anus	1	44	152	164 ± 54
"Prune belly" syndrome	1	44	294	164 ± 54
Hirschsprung's disease, total	1	47	94	239 ± 67
Atresia of ileum	1	49	155	239 ± 67
Omphalocele	2	49	163	239 ± 67
Diaphragmatic hernia	6	50	200	239 ± 67
Isolated malrotation	8	51	248	239 ± 67
Volvulus	1	52	161	239 ± 67
Exstrophy of urinary bladder	1	57	476	328 ± 77
Hepatoblastoma	1	75	308	351 ± 93
Hirschsprung's disease, distal colon	1	94	486	378 ± 90

*Mean ± 1 SD for corresponding crown-heel length group.

COMMENT

Determinations of small-intestine length have been made in both living and dead subjects, but variation between the two groups has been striking. The reported total length of the gastrointestinal tract is 450 cm in the living adult, of which 60% or 270 cm is contributed by the small intestine.[10] Reiquam et al[8] found that the average small-intestine length postmortem in a 160-cm adult was 555 cm, or twice that measured in living subjects. In the study by Reiquam et al and in our study, an intestinal length of about 270 cm was found in neonates. Loss of smooth muscle tone has been the given reason for the apparent postmortem elongation of the intestinal tract.[10] However, the frequent existence of intussusceptions seen at autopsies, especially those of children, has been taken as an indication that some degree of contraction of the small-bowel musculature occurs agonally.[14] It has been shown that stretch artifact of 4% in the adult small intestine and 14% in the large intestine can be produced manually.[15] In dealing with the more delicate pediatric tissues, the danger of stretching the gut during manipulation must be avoided.

It has been suggested that children with congenital heart disease may have an abnormally long small intestine.[8] In 13 instances of abnormally long bowel, defined as a small intestine-body length ratio greater than 7:1, six cases occurred in infants with congenital heart disease, four having involvement of the pulmonary valve. In the present study, no significant differences between mean small-intestine length (grouped by body length) obtained in 65 cases of congenital heart disease and in the remaining 118 children without heart disease were found.

In the present study, two patients with abdominal lesions had severely elongated small intestines. In one case of exstrophy of the urinary bladder, the small-intestine length was 476 cm (body length, 57 cm; expected intestinal length, 328 ± 77 cm). In one case of abdominal musculature deficiency or "prune belly" syndrome, the intestinal length was 294 cm (body length, 44 cm; expected intestinal length, 164 ± 54 cm).

The condition of shortened small intestine has also been examined.[3,7,8] In extreme cases of "congenital short small intestine" or "short gut syndrome," the morphologic features consist of a small-intestine length of 30 to 42 cm and malrotation.[7] The ratio of small-intestine length to body length would then be 1:1 or even less. None of the specimens in the present study were shortened to this degree, and none carried the clinical diagnosis of short-bowel syndrome. In the report by Reiquam et al,[8] of 16 children with small intestine-body length ratios less than 3:1, seven had malrotation and/or omphalocele. It was suggested that a patient with omphalocele and multiple anomalies has a longer small intestine than those without other anomalies.

That suggestion is weakly substantiated by two patients with omphalocele in the present study. The first, a patient with trisomy 18 syndrome, had a body length of 48 cm and an intestinal length of 190 cm, well within 1 SD from the mean. The second, with more minor anomalies (azygous continuation of inferior vena cava and hypoplastic right thumb), had an intestinal length of 136 cm, more than 1 SD less than the mean for his 50-cm body length.

Of the 29 cases involving an intra-abdominal lesion, the most severe shortening was seen in an infant with total aganglionosis or Hirschsprung's disease. This unoperated on infant whose body length was 47 cm had a 94-cm small intestine, far less than the normal range encountered in this study and the normal 5:1 ratio found by Reiquam et al.[8] This finding was in contrast to that of a 6-year-old patient (body length, 94 cm) with a long-standing colostomy for Hirschsprung's disease of the distal colon. The small-intestine length was 486 cm, slightly more than 1 SD greater than the mean for crown-heel length.

One case each of ileal atresia and volvulus had a short small intestine whose length was more than 1 SD lower than the mean. The intestinal lengths of other cases involving intra-abdominal lesions are given in the Table.

Albert W. Dibbins, MD, and Frank E. Sherman, MD, of the Departments of Surgery and Pathology, respectively, Children's Hospital of Pittsburgh, asked questions and gave advice during the early stages of the investigation. J. Bruce Beckwith, MD, Department of Laboratories, Children's Orthopedic Hospital and Medical Center, Seattle, provided advice in the final stages of the study.

References

1. Benson CD: Resection and primary anastomosis of the jejunum and ileum in the newborn. *Ann Surg* 142:478-485, 1955.

2. Benson CD, Lloyd JR, Smith JD: Resection and primary anastomosis in the management of stenosis and atresia of the jejunum and ileum. *Pediatrics* 26:265-272, 1960.

3. Konvolinka CW: Congenital short small intestine: A rare occurrence. *J Pediatr Surg* 5:574, 1970.

4. Pilling GP, Cresson SL: Massive resection of the small intestine in the neonatal period. *Pediatrics* 19:940-948, 1957.

5. Potts WJ: Pediatric surgery. *JAMA* 157:627-630, 1955.

6. Donnellan WL: Neonatal intestinal obstruction, in Swenson O (ed): *Pediatric Surgery*, ed 3. New York, Appleton-Century-Crofts, 1969, chap 34.

7. Yutani C, Sakurai M, Miyaji T, et al: Congenital short intestine. *Arch Pathol* 96:81-82, 1973.

8. Reiquam CW, Allen RP, Akers DR: Normal and abnormal small bowel lengths. *Am J Dis Child* 109:447-451, 1965.

9. Blankenhorn DH, Hirsch J, Ahrens EH Jr: Transintestinal intubation: Technique for measurement of gut length and physiologic sampling at known loci. *Proc Soc Exp Biol Med* 88:356-362, 1955.

10. Hirsch J, Ahrens EH Jr, Blankenhorn DH: Measurement of the human intestinal length in vivo and some causes of variation. *Gastroenterology* 31:274-284, 1956.

11. Louw JH: Congenital intestinal atresia and stenosis in the newborn: Observations on its pathogenesis and treatment. *Ann R Coll Surg Engl* 25:209-234, 1959.

12. MacMahon RA: Massive resection of intestine in infancy. *Aust NZ J Surg* 34:202-205, 1966.

13. Fisher RA: *Statistical Methods for Research Workers*. New York, Hafner Publishing Co Inc, 1958, chap 7 and 8.

14. Rezek PR, Millard M: *Autopsy Pathology*. Springfield, Ill, Charles C Thomas Publisher, 1963, chap 15.

15. Unherhill BML: Intestinal length in man. *Br Med J* 4950:1243-1246, 1955.

Intravenous Aminophylline Therapy for Asthma

A Comparison of Two Methods of Administration in Children

Paul Goldberg, MD; Fred Leffert, MD; Mario Gonzalez, PhD; Larry Gogenola, MS; Gary O. Zerbe, PhD

• Eleven asthmatic children were given intravenous aminophylline by two methods of administration: a 6 mg/kg loading dose followed by a 1.1 mg/kg/hr continuous infusion, or a bolus of 4 mg/kg given every four hours. Expiratory flow rates (forced expiratory volume at 1 s and expiratory flow at 50% of vital capacity) were recorded at intervals for 24 hours with each regimen. Although the intermittent administration of aminophylline produced a substantial improvement, there was a significantly greater pulmonary response to continuous infusion.

(*Am J Dis Child* 134:596-599, 1980)

The use of intravenous (IV) aminophylline in the treatment of asthma has become widely accepted in contemporary pediatric practice. Although it appears to be an effective agent for treatment of acute exacerbations of asthma,[1] an optimal method of administration has not been defined. Currently, two approaches are in use: injection of a bolus dose at regular intervals, or injection of a loading dose followed by constant infusion of the drug. This study compares the effects of these two methods in a group of asthmatic children.

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Reprints not available.

SUBJECTS AND METHODS

The subjects were 11 children (six girls and five boys) between the ages of 7 and 15 years. All subjects met the criteria for reversible obstructive airway disease of the American Thoracic Society.[2] All were inpatients at the National Jewish Hospital, Denver, for treatment of perennial asthma, and had been shown to require regular daily use of oral bronchodilators for maintenance of good pulmonary function. None had received corticosteroids for at least two weeks prior to the study. Informed consent was obtained from children and their parents.

Each subject was studied on two days, with a one-week interval between study days. Studies were conducted in the pediatric clinical research unit, and began at 8 AM on each study day. All medication was withheld for at least 12 hours before beginning each trial. A child was admitted to the study only if his baseline expiratory flow rates (1-s forced expiratory volume [FEV_1] and forced expiratory flow at 50% of vital capacity [FEF_{50}]) were less than 80% of predicted, and (for the second day) if flow rates were within 20% of baseline rates for the first day. Children experiencing respiratory distress and requiring additional medication were discharged from the study. After baseline pulmonary function and serum theophylline measurements were obtained, each subject was randomly assigned to a treatment protocol, with the other protocol used on the second study day.

Continuous infusion consisted of a loading dose of 6 mg/kg of aminophylline, which was given in a 25-mL volume during five minutes by infusion pump, followed by a continuous infusion of 1.1 mg/kg/hr by the same apparatus. The infusion was continued for 24 hours. Intermittent administration consisted of a dose of 4 mg/kg of aminophylline in a 25-mL volume given during five minutes by infusion pump. This was repeated every four hours for 24 hours (six doses). The protocol for continuous infusion followed the recommendations of Piafsky and Ogilvie,[3] while the intermittent administration regimen has been the customary approach at National Jewish Hospital for several years.

Subjects had catheters placed in peripheral veins in both arms, so that drug administration and blood sampling for serum theophylline levels were accomplished through separate systems. Children were observed by nurses during the entire study period, and pulse, blood pressure, auscultation of the chest, and inquiries as to dyspnea, abdominal distress, or CNS stimulation were recorded every four hours. Blood specimens were obtained for measurement of serum theophylline concentration, and spirometry was performed immediately before beginning aminophylline infusion, and 1, 4, 8, 12, and 24 hours afterward. For the intermittent administration protocol, these measurements (except at one hour) were obtained immediately before the next dose, and so represent trough levels of theophylline.

Forced vital capacity maneuvers were performed with a wedge spirometer, with recording of maximal expiratory flow-volume curves on an X-Y plotter. The better of two efforts was used for determination of the FEV_1 and the FEF_{50}.

Blood samples for serum theophylline measurement were obtained from a catheter placed in a peripheral vein. Serum was separated and frozen for later analysis by high-pressure liquid chromatography. The serum clearance rate was calculated for each patient from the continuous infusion data. This calculation consisted of dividing the maintenance rate of infusion by the mean steady-state serum concentration (average of the values at 4, 8, 12, and 24 hours).

The statistical tests employed for evaluation of the pulmonary function data were introduced by Zerbe and Walker[4] for the

purpose of comparing mean growth curves. More recently, Zerbe[5,6] has refined these techniques and indicated their applicability to dose-response and time-response curves. They are particularly well suited to the problem of comparing pulmonary function curves during an interval of time without the need for separate t tests at each point within the interval. They are also nonparametric tests requiring no distribution assumptions, particularly appealing when the end point is a percent change from baseline.

RESULTS

The pulmonary responses to the two methods of treatment are shown in Fig 1 to 5 and in Table 1. Figures 1 to 4 display group data, while Fig 5 shows the responses of individual subjects.

Figure 1 displays the mean FEV_1 response curves. The FEV_1 response to continuous administration was greater than that for intermittent dosage, but not significantly so

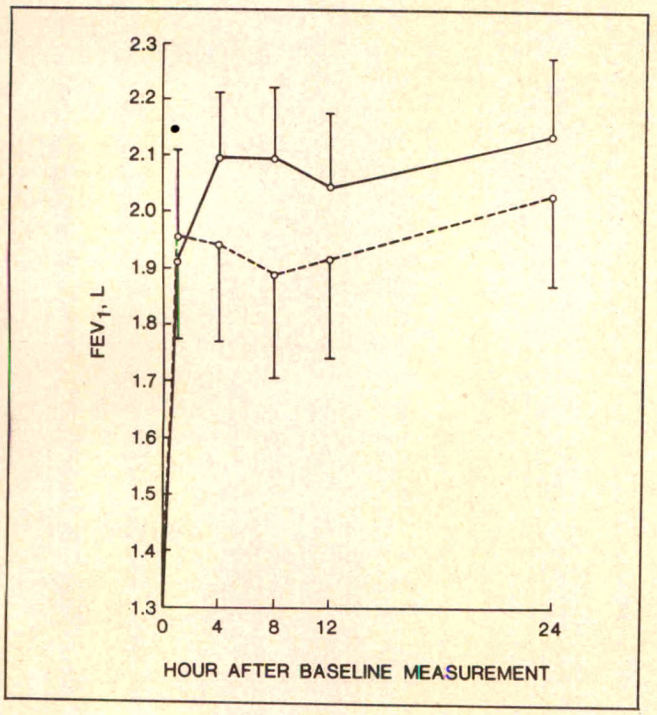


Fig 1.—Mean 1-s forced expiratory volume (FEV_1) responses to continuous (solid line) and intermittent (broken line) treatment ±1 SEM.

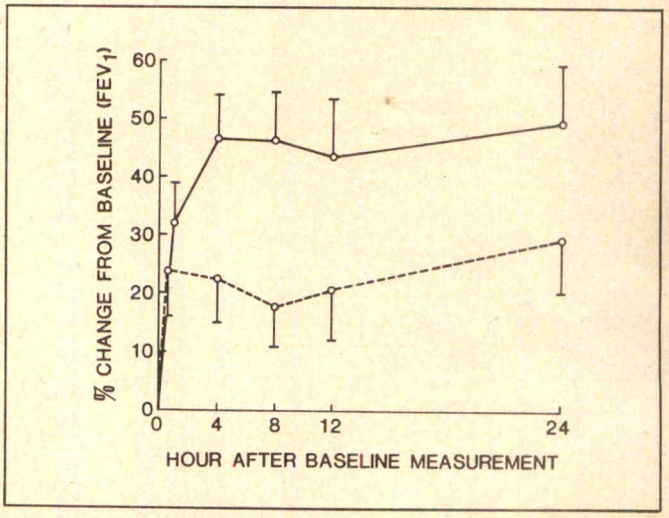


Fig 2.—Mean percent change in 1-s forced expiratory volume (FEV_1) for continuous (solid line) and intermittent (broken line) treatment ±1 SEM.

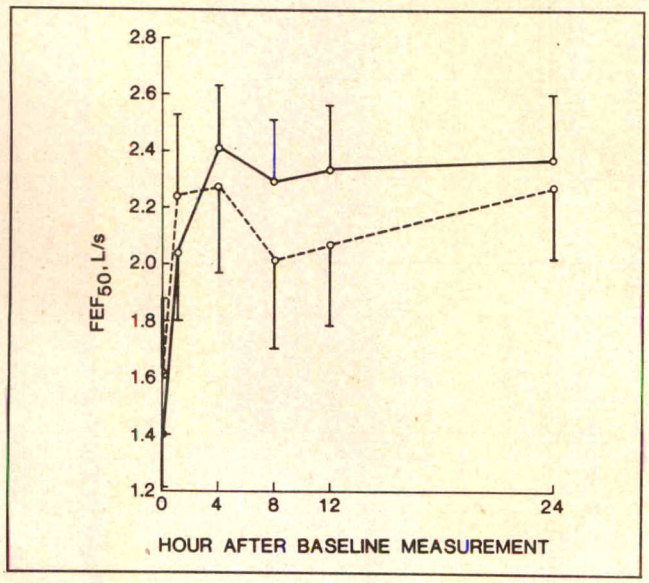


Fig 3.—Mean forced expiratory flow at 50% of vital capacity (FEF_{50}) responses to continuous (solid line) and intermittent (broken line) treatment ±1 SEM.

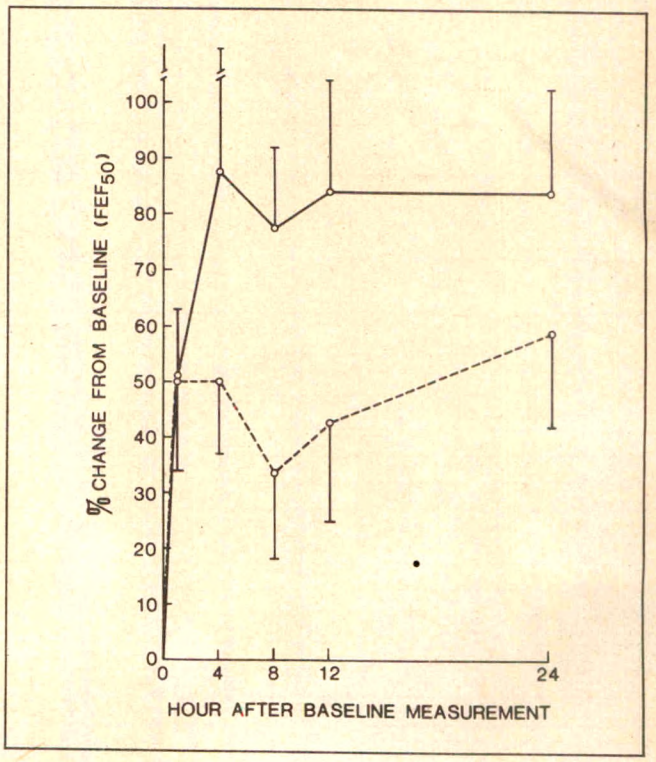


Fig 4.—Mean percent change in forced expiratory flow at 50% of vital capacity (FEF_{50}) for continuous (solid line) and intermittent (broken line) treatment ±1 SEM.

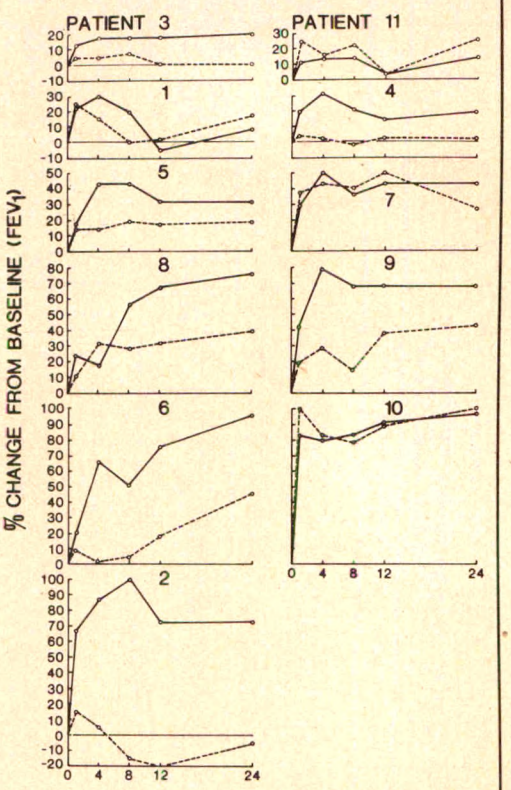


Fig 5.—Responses of individual subjects (percent change in 1-s forced expiratory volume [FEV_1]) to continuous (solid line) and intermittent (broken line) treatment.

(P = .1). Although the 0.14-L difference between the baselines for the two groups was also nonsignificant (P = .08), the comparison was made again after adjusting for the baselines. Figure 2 displays mean percent change from baseline FEV_1 response curves. After this adjustment, the response curve for continuous administration is significantly elevated over that for intermittent treatment (P = .01) during the 24-hour period.

Similarly, Fig 3 and 4 display FEF_{50} response curves, and mean percent change from baseline FEF_{50} response curves, respectively. On the absolute scale, the continuous and intermittent response curves are not significantly different (P = .20), nor is the difference between baseline values (P = .08). However, when viewed as percent change from baseline, the response curve for continuous administration is significantly elevated over that for intermittent dosage (P = .02).

Figure 5 shows the responses of individual children in terms of percent change in FEV_1. There was a great deal of variability among subjects,

Table 1.—Pulmonary Responses*

	FEV_1, L, at Hour						FEF_{50}, L/s, at Hour					
Treatment	0	1	4	8	12	24	0	1	4	8	12	24
Continuous	1.50 ± .14	1.90 ± .13	2.10 ± .12	2.09 ± .13	2.04 ± .13	2.13 ± .14	1.41 ± .20	2.04 ± .24	2.41 ± .22	2.30 ± .21	2.34 ± .22	2.37 ± .23
Intermittent	1.64 ± .17	1.95 ± .16	1.94 ± .17	1.89 ± .17	1.91 ± .17	2.03 ± .15	1.62 ± .26	2.24 ± .29	2.27 ± .31	2.02 ± .30	2.07 ± .28	2.27 ± .24

*Mean ± 1 SEM.

Table 2.—Pharmacokinetic Data

	Serum Theophylline Levels, μg/mL												
	Intermittent at Hour						Continuous at Hour						Clearance,
Patient	0	1	4	8	12	24	0	1	4	8	12	24	mL/hr/kg
1	1.5	4.3	3.1	5.0	6.2	4.8	6.7	13.2	12.1	11.2	10.2	9.7	101.8
2	0.5	4.9	3.0	3.7	3.7	6.2	1.4	10.0	10.0	10.3	9.4	10.5	109.4
3	0.8	7.9	4.4	5.2	6.6	5.3	1.2	10.5	9.3	10.5	10.7	12.3	102.8
4	7.9	14.3	10.3	11.3	8.8	11.9	7.0	15.2	18.8	18.6	18.9	20.0	57.7
5	1.3	5.3	4.9	6.6	7.3	10.0	2.5	11.4	12.8	12.6	12.5	16.4	81.0
6	1.7	8.0	ND*	7.4	7.4	11.0	3.3	12.9	14.8	12.2	14.2	23.3	68.2
7	3.6	7.5	6.2	5.0	8.1	9.4	4.0	14.0	13.4	15.2	13.8	13.6	78.6
8	4.6	18.6	6.2	7.8	8.9	12.9	5.7	15.4	16.9	15.9	16.7	ND	66.7
9	2.5	9.0	4.2	9.5	6.7	8.0	2.8	10.3	11.7	12.9	12.4	10.2	93.2
10	5.2	9.7	7.3	7.8	8.9	12.3	6.6	12.1	13.4	14.9	ND	17.1	72.7
11	3.4	6.2	5.0	6.9	6.4	9.0	5.1	14.4	15.8	14.4	14.1	18.9	69.6

*ND indicates not done.

with a very marked superiority of continuous over intermittent treatment in some children (particularly subjects 2, 6, and 9), while others showed little difference in their responses (eg, subjects 7 and 10). No subject showed a greater response to intermittent than to continuous treatment.

Six children had wheezing at the beginning of both study days, which resolved after treatment began. No children had objective (pulse, blood pressure) or subjective (CNS or gastrointestinal) findings suggesting theophylline toxicity while on either regimen. Pharmacokinetic data are summarized in Table 2.

COMMENT

Interpretation of these data requires consideration of several factors that may have influenced the results of the study. The subjects, although experiencing active disease requiring bronchodilator treatment, were not suffering from status asthmaticus. The study of patients with status asthmaticus would have introduced several difficulties, including lack of control of prestudy medication, the need for concomitant use of sympathomimetic drugs, and difficulty in obtaining satisfactory spirograms in distressed children. We therefore chose to compare the bronchodilating efficacies of these regimens in a more controlled setting than is possible in the actual clinical situation.

It will also be noted that the study design appears to favor the demonstration of greater efficacy for the continuous infusion method. Spirometry was performed when the serum theophylline concentration was at a trough level during the intermittent regimen. Also, the total amount of aminophylline given during the continuous infusion was greater—6 vs 4 mg/kg at the onset, and a total dose of 32.4 vs 24.0 mg/kg during the 24 hours. The 4 mg/kg dose was selected because it represented the customary therapy at our institution, and it was this traditional approach that we wished to compare with the newer technique. Pulmonary function measurements were made at trough levels for two reasons. Since serum theophylline concentration appears to correlate with therapeutic efficacy only insofar as it is a reflection of tissue level of the drug,[7] selection of optimal time for sampling becomes complicated, since a sample taken too soon may give a spuriously high level during the distributive phase. The trough level measurement also reflects our feeling that the lowest level to which pulmonary function is allowed to fall during treatment may be the most clinically relevant consideration.

Although medication had been withheld for at least 12 hours prior to the study days, all subjects had theophylline detected in the baseline serum sample (Table 1). Although these levels were very low (mean of 3.0 μg/mL for intermittent vs 4.2 μg/mL for continuous administration), it is possible that this difference also contributed to the better response shown in the continuous infusion group.

After taking all of these factors into account, it was somewhat surprising that, excepting subjects 2, 6, and 9, the difference in response between the two methods was not impressive for most of the children, even though the inclusion of these three subjects gives a statistically significant difference for the mean group responses.

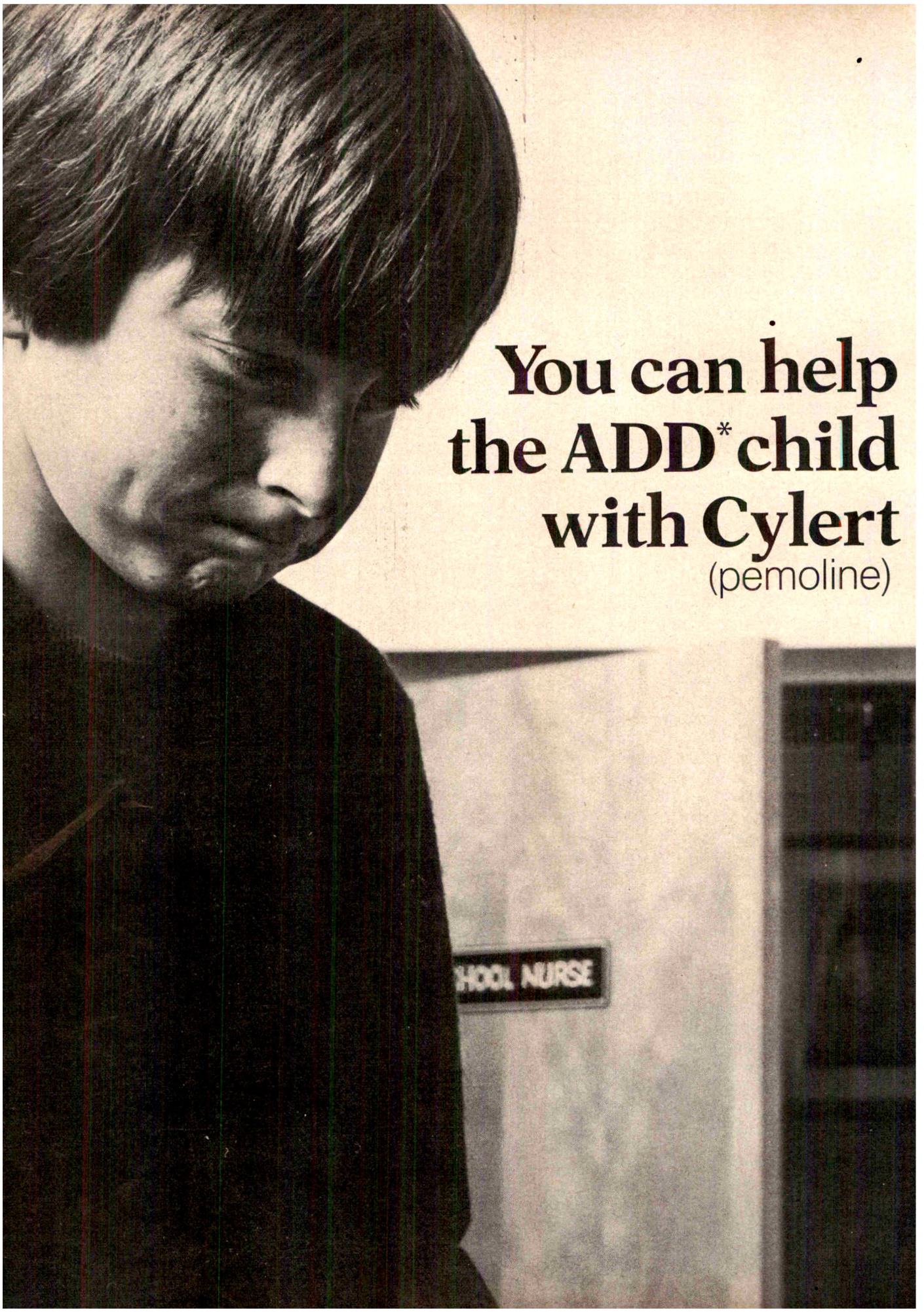
The finding of a wide range of clearance rates for theophylline in this group of children is in agreement with the results of more extensive pharmacokinetic studies.[8] Following the recommendations of Piafsky and Ogilvie[3] for aminophylline infusion led to the maintenance of serum levels in the "therapeutic range" (10 to 20 μg/mL) in all subjects. However, it should be noted that if their higher dose regimen (9 mg/kg loading followed by 1.65 mg/kg/hr) had been used, several subjects would have attained serum levels well over 20 μg/mL. We considered the possibility that serum clearance rate might be a major determinant of whether a subject gave similar or different responses to the two treatment protocols, but were unable to demonstrate such a relationship. For instance, subjects 2 and 3 had very similar clearance rates, but strikingly different pulmonary response patterns.

Although intermittent injection of aminophylline at 4 mg/kg was less efficacious than continuous administration in improving pulmonary function, it did give a clinically significant response (≥ 20% increase in FEV_1). Therefore, it appears to be an effective technique for asthma therapy, although perhaps no longer the method of choice. A problem inherent in continuous administration is the need for reliable maintenance of the infusion during long periods of time, with regular monitoring of the amount of drug infused. The serum theophylline level of 23.3 μg/mL noted in subject 6 was most likely due to human or mechanical error in the maintenance of a steady infusion rate. In situations where adequate personnel and equipment are not available, intermittent administration may represent a simple safe alternative.

The results of this study suggest that use of a loading dose followed by a continuous infusion of aminophylline will, on the average, give a better pulmonary response than intermittent injection of the drug, at least at the dosages used herein. The infusion technique therefore appears to be the method of choice for IV aminophylline therapy. Intermittent administration may be a useful alternative approach in clinical settings in which the infusion technique cannot be safely and reliably implemented.

References

1. Pierson WE, Bierman CW, Stamm SJ, et al: Double-blind trial of aminophylline in status asthmaticus. *Pediatricus* 48:642-646, 1976.
2. American Thoracic Society: Definitions and classifications of chronic bronchitis, asthma and pulmonary emphysema. *Am Rev Respir Dis* 85:762-768, 1962.
3. Piafsky KM, Ogilvie RI: Dosage of theophylline in bronchial asthma. *N Engl J Med* 292:1218-1222, 1975.
4. Zerbe GO, Walker SH: A randomization test for comparison of groups of growth curves with different polynomial design matrices. *Biometrics* 33:653-657, 1977.
5. Zerbe GO: Randomization analysis of the completely randomized design extended to growth and response curves. *J Am Stat Assoc* 74:215-221, 1979.
6. Zerbe GO: Randomization analysis of randomized blocks extended to growth and response curves. *Commun Stat Theory Meth* 2:191-205, 1979.
7. Levy G, Koysooko R: Pharmacokinetic analysis of the effect of theophylline in asthmatic children. *J Pediatr* 86:789-793, 1975.
8. Ellis EF, Koysooko R, Levy G: Pharmacokinetics of theophylline in children with asthma. *Pediatrics* 58:542-547, 1976.



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DESCRIPTION: CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one.

Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg./ml.) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg./ml.

CYLERT (pemoline) is supplied as tablets for oral administration.

CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

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Review

Acute Febrile Mucocutaneous Lymph Node Syndrome

Richard Yanagihara, MD, James K. Todd, MD

More than a decade ago, Tomisaku Kawasaki, a Japanese pediatrician, described an acute exanthematous disease characterized by persistent fever, mucous membrane hyperemia, cervical lymph node enlargement, and periungal desquamation in 50 infants and children who had been seen during the preceding six-year period at the Japan Red Cross Medical Center in Tokyo.[1] Individually the clinical and laboratory features seemed not unlike those of other mucocutaneous syndromes and exanthematous illnesses of childhood, but Kawasaki decided that the constellation of findings was distinctive and constituted a hitherto undescribed clinical entity. The disease was designated mucocutaneous lymph node syndrome (MCLS).[1]

After this description, numerous cases were reported throughout Japan, and in 1970 the Research Committee of MCLS, supported by the Ministry of Health and Welfare of the Japanese government, was organized. The primary purpose of this group was to conduct and to coordinate investigations involving the etiology and the clinical, pathological, and epidemiological features of the disease. Much has since been learned about this syndrome, but there remain major gaps in our understanding about its etiology, pathogenesis, natural history, and treatment.

In recent years MCLS has been the subject of editorials,[2-6] reviews,[7-10] and symposia.[11-12] In 1976, the MCLS study group adopted the eponym Kawasaki's disease in place of the acronym MCLS, thus accepting it as a nosological entity. For some, however, there still remain uncertainties about whether this symptom-complex actually constitutes a novel, discrete clinicopathologic entity.[13-17] Does the designation MCLS denote a heterogeneous population of patients with a variety of previously described infectious or noninfectious illnesses characterized by mucocutaneous manifestations, or does it truly define a homogeneous population of patients with a distinct, hitherto undescribed clinical illness? What is the relationship between this syndrome and other mucocutaneous and vascular disorders, particularly infantile polyarteritis nodosa (IPN)? More specifically, are the clinical or histological features of MCLS sufficiently distinctive to differentiate them from those of IPN? Finally, would it be more appropriate to refer to this aggregate of signs and symptoms as a syndrome or as a disease? We will review the available data in an attempt to answer some of these questions and to determine the position MCLS occupies in relation to other acute febrile mucocutaneous syndromes.

CLINICAL FEATURES

The diagnostic criteria established by the MCLS study group were based on Kawasaki's original detailed description.[1] They are as follows: (1) fever of five or more days; (2) bilateral congestion of the ocular conjunctivae; (3) changes of the mucous membranes of the oral cavity, including erythema, dryness, and fissuring of lips; erythema of the tongue and prominence of the papillae; diffuse reddening of the oropharyngeal mucosa; (4) changes of the peripheral extremities, including reddening and indurative edema of the hands and feet, and membranous periungal desquamation; (5) polymorphous exanthem; (6) acute nonsuppurative swelling of the cervical lymph nodes. The presence of five of these six principal criteria, or, more

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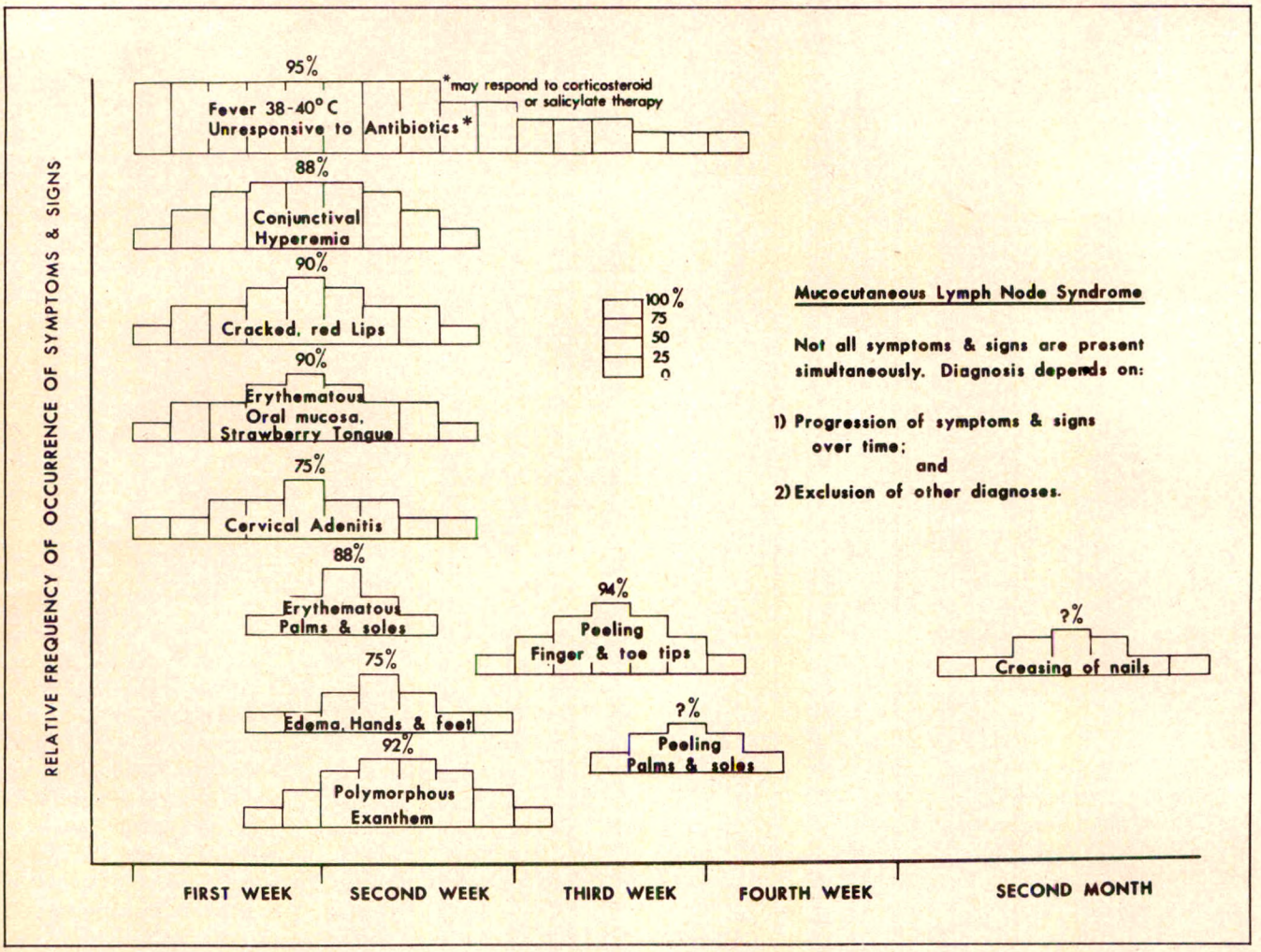


Fig 1.—Clinical manifestations of mucocutaneous lymph node syndrome (percentages from Kawasaki et al[23]).

appropriately, the presence of prolonged fever and four of the remaining five criteria, in the absence of evidence implicating other well-known diseases, is required to establish the diagnosis of MCLS.

According to the case definition then, MCLS is strictly a clinical diagnosis and further it is a diagnosis of exclusion. The symptom-complex evolves over time such that all of the clinical features are not apparent simultaneously (Fig 1).

Mucocutaneous lymph node syndrome is a disease of infants and young children. The age of peak incidence is nine to 12 months in Japan[18] and about 3 years in the United States.[9,19] There is a slight but definite male predominance.[9,18,19]

Generally affected patients appear mildly to moderately ill. Fever, with temperatures ranging from 38.5 to 40.5 °C, is usually the most prominent symptom and is often the reason for hospitalization. The pattern of pyrexia is usually hectic and is totally unresponsive to antibiotic therapy. In most cases, fever persists for eight to 18 days, although prolonged courses of up to five weeks have been reported.[20] It is the height and persistence of fever beyond the usual three- to five-day duration expected for most self-limited viral illnesses in the young child that may first suggest the possibility of MCLS to the clinician.

Shortly after the onset of fever, bilateral congestion of the ocular conjunctivae develops. There is no suppuration or pseudomembrane formation, chemosis, or keratitis. This may be accompanied by diffuse and marked reddening of the lips and the oropharyngeal mucosa, without aphthous ulcerations or hemorrhagic bullae. The vermilion borders of the lips are frequently dry and fissured. Prominent lingual papillae ("strawberry tongue") may also be observed.

In the later half of the first week of illness, marked erythema of the palms and soles and brawny, nonpitting, indurative edema of the hands and feet may develop. Often, an erythematous, macular rash appears, originating frequently on the extensor surfaces of the arms and legs and progressing centripetally. The individual macules or maculopapules enlarge rapidly and frequently become coalescent. The cutaneous eruption is characteristically polymorphous and can be primarily morbilliform (maculopapular), scarlatiniform, or multiform in appearance. Typical iris or target

lesions are sometimes reported,[21,22] but crusts, vesicles, or bullae are not seen and pruritus is distinctly uncommon. The exanthem usually fades within a week, but occasionally may persist or recur.

During the later part of the second and into the third week of illness—usually after the resolution of fever—an unusual membranous desquamation begins in the subungal and periungal regions of the fingers and toes. This finding is especially but not exclusively characteristic of MCLS. Exfoliation is usually minimal or absent in other anatomical sites. Late in the convalescent phase (one to two months) transverse grooves or furrows may develop across the nailbed.[1,23]

Nonpurulent, often unilateral, cervical lymph node enlargement (1.5 cm or more in diameter) is noted commonly at the time of initial presentation or thereafter. Cervical lymphadenopathy can be of such marked degree that retropharyngeal or peritonsillar abscess may be suspected.[24] The mass diminishes in size usually at the time of defervescence. Generalized lymphadenopathy does not occur.

In addition to the six cardinal criteria, other clinical features, such as diarrhea, arthralgia and arthritis, meatitis, tympanitis, photophobia, meningeal irritation, and pneumonia, are often noted during the acute stage of illness. Diarrheal stools are nonbloody and usually nonmucoid. Either arthralgia or frank arthritis with erythema, swelling, warmth, pain, and decreased range of motion may be a prominent feature.[21,23,25-28] Large joints, particularly elbows, wrists, knees, and ankles, are more frequently involved, and oligoarticular involvement is usual.

Meatal inflammation, as evidenced by pyuria on clean-voided urine specimens, is also a common finding (see "Laboratory Findings"). Meatal ulcers occur rarely.

Other findings, such as hydrops of the gallbladder,[29,30] convulsions,[31] encephalopathy,[21,31] jaundice,[23] pleural or pericardial effusions,[32] have been reported but are uncommon.

Probably the most alarming feature of MCLS is the cardiac and coronary arterial involvement. Its actual incidence is unknown. Arrhythmia, myocarditis, pericarditis, congestive heart failure, and myocardial ischemia and infarction have all been reported. Cardiac signs (eg, shock, arrhythmia, distant heart sounds, gallop rhythm) may appear as early as the first week of illness or during prolonged convalescence. While the outcome is generally favorable, approximately 1.5% of children die[18]; deaths usually occur within two months of the onset of illness,[33,34] but may occur years later.[35,36]

EPIDEMIOLOGY

Since the initial description by Kawasaki[1] and the publication of his findings in the English language,[23] there has been a profusion of case reports from many countries. The first cases to be reported outside Japan were from South Korea[37] and Hawaii.[38] The syndrome has since been recognized in Canada,[35,39,40] Mexico,[9] Hungary,[28] Switzerland,[41] West Germany,[42] England,[43-47] the Netherlands,[13,14] India,[26] Kuwait,[27] the Phillipines,[9] Australia,[48] Spain,[9] France,[9] Jamaica,[9] Italy,[49] Greece,[50] Sweden,[51] Turkey,[52] Scotland,[53] Belgium,[54,55] and the continental United States.*

While the Center for Disease Control (CDC) has been gathering information about cases of MCLS occurring in the United States since 1975, most of our present knowledge about the epidemiology of this syndrome comes from the Japanese national surveys. Nationwide retrospective surveys have been conducted by the MCLS study group biennially beginning in 1970.[18,68] Questionnaires and the diagnostic guidelines for MCLS were sent to the pediatric departments of all hospitals with more than 100 patient beds (1,688 hospitals). The response rate was about 40% to 60% for each survey. Data from the 1978 survey are presently being tabulated. Preliminary analysis indicates that the incidence of MCLS has continued to increase and has reached nearly epidemic proportions. About 18,000 cases (15,435 definite and 2,428 probable) have been registered in Japan since the first nationwide survey (I. Shigematsu, MD, verbal communication, 1979). This represents an annual incidence of approximately 2,700 cases in recent years.

It is still uncertain whether the findings of the Japanese epidemiological investigations are applicable to the United States or to other countries. However, recent analysis of the more than 200 MCLS cases submitted to the CDC[9,19] has revealed several epidemiological similarities between the Japanese and American cases. There appears to be no definite seasonal pattern (with the possible exception of a slightly higher incidence during the warmer months in Japan) or geographical limitation. Cases have been registered in all 46 prefectures of Japan,[18] and the CDC has learned of cases from the District of Columbia, Puerto Rico, and 31 of the 50 states.[9,19] Rural or urban residence, altitude, topography, and proximity to water have not appeared to be determining factors in Japan.[18]

Male children tend to be affected more frequently both in Japan (male-to-female ratio 1.5:1)[18] and in the United States (1.8:1)[19] but the age of peak incidence is lower in Japan, where 85% of the children are younger than five years.[18,68]

Thus far, of the American cases, 57% have been in whites, 18% in blacks, and 25% in Orientals, predominantly of Japanese ancestry.[19] Although the cases are rare, secondary cases in twins and in siblings[43,69] and recurrences[21,70] have been reported.

Epidemiologically there has been little progress beyond the purely descriptive stage. An in-depth case-control study conducted by Yanagawa and Shigematsu[68] revealed that several factors were more prevalent among index cases than in their age- and sex-matched, hospitalized control subjects: previous history of cervical lymphadenitis, pharyngitis; vaccinations with Bacille Calmette-Guerin, vaccinia virus, poliovirus, diptheria-tetanus-pertussis; and maternal drug use during pregnancy (for allergy, respiratory infection, and vomiting). Differences in dietary habits, brands of milk, types of detergents, prenatal and neonatal problems, birthweight of

*References 20,22,24,25,29-32,36,56-67.

infant, and maternal age at the time of delivery between index cases and controls were not statistically significant.

LABORATORY FINDINGS

There is no single or battery of laboratory tests that is diagnostic for MCLS, but levels of acute-phase reactants, as measured by total WBC count, ESR, C-reactive protein, and serum α_2-globulin, are consistently elevated or increased. Leukocytosis (total WBC count > 15,000/cu mm) with leftward shift is commonly seen early in the illness and usually persists for one to three weeks. Leukemoid-type responses are observed rarely.[1,21,56]

The ESR is frequently elevated and the C-reactive protein is strongly positive at the time of initial presentation. In one series, the ESR appeared to have prognostic value: it tended to be higher and to remain elevated in patients in whom coronary artery stenosis or aneurysm developed.[71]

Other hematological abnormalities include mild normocytic, normochromic anemia and thrombocytosis. The latter finding becomes maximally apparent during the second and third weeks of illness.[21,25,30,57,72] Platelet aggregation is increased and may remain abnormal for months.[72] Thrombocytopenia has not been reported, and, if present, should suggest diagnoses other than MCLS.

Examination of clean-voided urine sediments typically reveals a few to many leukocytes during the acute phase of illness.[1,20,21,24-27] Urine obtained by suprapubic puncture, however, is reportedly free of WBCs.[21,58] Hematuria is observed infrequently,[21,39,43] whereas proteinuria occurs commonly.[1,21,39,42,59]

Mild CSF pleocytosis with lymphocytic predominance is occasionally seen.[1,20,21,25,31,39,60] Concentrations of CSF glucose and protein are normal.

Elevations in levels of serum bilirubin[30,36,56,59] and transaminases[24,27,30,36,60,61] may be observed. Serum electrolytes, urea nitrogen, and creatinine levels are normal.

There is no evidence for autoimmune phenomena: lupus erythematosus cell preparation† and rheumatoid factor‡ are negative; antinuclear antibodies§ and antibodies to DNA,[54] mitochondria,[54] striated muscle,[54] and myocardial sarcolemma[54] are absent. Quantitative immunoglobulin levels are generally normal for age, but elevations in class-specific immunoglobulins may be found.

Cultures of respiratory secretions, urine, feces, blood, CSF, pericardial fluid, lymph node aspirates, and postmortem tissues, as well as serological studies, for bacterial and nonbacterial agents are usually negative. Sporadic reports of the isolation of microorganisms from patients with MCLS have appeared, but their association with the disease process remains obscure (see "Etiology and Pathogenesis").

Transient abnormalities in ECG tracings, namely, prolongation of PR and QTc intervals, flattening of T waves, depression of ST segments, have been reported in 60% to 90% of Japanese cases.[73-77] Changes in ECG patterns may be as common in American cases.[78] Myocardial infarction patterns are encountered infrequently.

Coronary angiograms are reportedly abnormal in 30% to 60% of Japanese patients studied within two months after the onset of illness.[73-77,79] Abnormalities range from mild tortuosity and dilation of coronary arteries to aneurysm formation and marked stenosis. Spontaneous regression of coronary arterial lesions has been documented by serial angiograms.[73,74,77]

Cardiomegaly[74,76,79] and abnormal left ventricular function[75] (decreased ejection fraction, increased end-diastolic volume, elevated end-diastolic pressure, or mitral regurgitation) have been observed in patients with MCLS with abnormal coronary angiograms.

PATHOLOGY

Initially, MCLS was thought to be a relatively benign, self-limiting condition.[1] However, shortly after Kawasaki's original description, disease-related fatalities became apparent.[80,81] Most of the deaths occurred suddenly and quite unexpectedly during convalescence and were usually due to rupture of coronary aneurysms or to coronary thromboarteritis.[33,36,82]

The epidemiological features of 54 fatal cases of MCLS have been reviewed by Tanaka and co-workers.[33,34] Nearly 76% of the fatalities were in children younger than 2 years and only 5.4% were in children older than 6 years. While late deaths (over 180 days after the onset of illness) were registered, the majority of deaths (57%) occurred between the tenth and 29th days of illness. The male-to-female ratio of fatal cases was 3:1.

Heart and Coronary Vessels

The cardiovascular system is principally involved. Abnormalities apparent on gross and microscopical examination of necropsy materials are confined generally to the heart and the main coronary arteries. The heart is frequently enlarged and hypertrophied.[21,33,34,83] Numerous small, beadlike aneurysms are commonly found along the major coronary arteries, which are usually tortuous and dilated.[33,34,83] The coronary ostia may be partially or completely occluded by thrombi.[33,34,82,83]

The cardiac lesions of MCLS have been classified according to the duration of illness at the time of death.[83] If death occurs during the very acute phase of illness (stage I: zero to nine days), the pathological features, while profound, are limited to perivasculitis or microvessels (arterioles, venules, and capillaries) and of small arteries, including the vasa vasorum of the main coronary arteries. Aneurysms or stenoses are not evident. Acute pericarditis, interstitial myocarditis, and endocarditis may be observed.

Characteristic features of stage II (12 to 25 days) include panvasculitis and perivasculitis of the main coronary arteries, with stenosis or obstruction and aneurysm formation, pericarditis, interstitial myocarditis and endocarditis, and phlebitis of larger veins. Fibrinoid necrosis of the media occurs rarely.

Partial or total occlusion of the main coronary arteries due to granu-

†References 21,23,27,30,36,40,43,62,63,73.
‡References 20,21,23,27,30,39,42,60-62.
§References 20,21,23,30,36,39,40,42,43,54,60-63.

lating thrombi or to marked intimal proliferation is typically observed in patients who die 28 to 31 days after the onset of illness (stage III). Angiitis or microvessels is absent, and myocarditis and endocarditis are less apparent.

Typically, severe scar formation and stenosis of the main coronary arteries are seen in stage IV (duration of illness at death, more than 40 days). Myocardial fibrosis and endocardial fibroelastosis are prominent. Inflammatory or ischemic changes of the atrioventricular conduction system (atrioventricular node, His bundle, left and right bundle branches) are observed commonly during all stages and are thought to be responsible for fatal arrhythmias.[83]

Deposits of albumin, fibrinogen, and IgG in the adventitia and tunica media of coronary arteries have been detected by immunofluorescence technique[84]; IgG has also been demonstrated within cardiac myofibrils.[84] It is unclear whether the localization of albumin, fibrinogen, and IgG is due to immune-complex deposition or to exudation of these proteins into areas of fibrinoid degeneration.

Other Vessels

Other small and medium-sized arteries (eg, renal, periadrenal, iliac, testicular, splenic) may exhibit intimal thickening, round cell infiltration, cicatrization, and, rarely, fibrinoid necrosis.[33,34,82]

Thymus

Autopsy records of fatal cases of MCLS indicate that the thymus is greatly reduced in size.[33,34] The medullary substance contains poorly formed Hassall's corpuscles. The number of lymphocytes in the cortex is greatly reduced and spindle cells are prominent. Whether thymic involution is the result of the acute illness or of corticosteroid administration in the more severe cases is unknown.

Lymph Nodes

Histological abnormalities in cervical lymph node biopsy specimens are nonspecific. Swelling of the endothelial cells and proliferation of immunoblast-like cells around postcapillary venules, and hyperplasia or reticulum cells have been described.[29,33,34,54]

Skin

Examination of skin biopsy specimens taken during the acute phase of illness has disclosed dilations of the intrapapillary capillary loops, endothelial fenestrations and necrosis, dermal edema, and perivascular cell infiltration consisting primarily of lymphocytes, marcophages, and mast cells.[85] These findings are nonspecific, but partly resemble those seen in delayed-type hypersensitivity reactions.

Pathology of Infantile Polyarteritis Nodosa (IPN)

The pathological findings of IPN have been well described.[15,86-88] Severe arteritic involvement and aneurysm formation of the main coronary arteries are typically found. Other musculoelastic arteries (eg, renal, periadrenal, splenic, pancreatic, pulmonary) are involved commonly. Arterial lesions are most often located at the bifurcations of vessels, and various stages of the arteritic process can be seen concomitantly. Fibrinoid necrosis in the media of medium-sized arteries tends to be inconspicuous or absent.[15,86-88] Endarteritis, a characteristic feature of the exudative phase that is marked by intimal proliferation, is prominent.

Myocardial inflammation in association with necrosis, and mild to moderate phlebitis, particularly of pulmonary veins, may also be observed.[15]

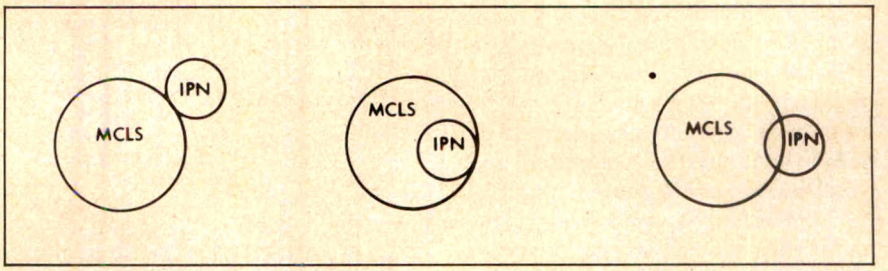
Relationship Between Fatal MCLS and IPN

The pathological similarities between fatal MCLS and IPN have been recognized by several investigators,[15,33,34,51,83] but the exact relationship of these conditions has not been firmly established. Specifically, the question of whether fatal MCLS actually represents IPN needs clarification. In part, the difficulty in resolving this issue rests on how the diagnosis of each condition is usually made. Infantile polyarteritis nodosa is rarely suspected or diagnosed prior to death[87,89]; it is a pathological diagnosis based almost entirely on morphological features. Conversely, MCLS is a clinical diagnosis based on a series of signs and symptoms.

There are several ways in which the relationship between fatal MCLS and IPN can be expressed schematically. The diagrams in Fig 2 may be used to represent the pathological relationship between these two conditions: the first postulate is that fatal MCLS and IPN are discrete entities that are mutually exclusive; the second is that fatal MCLS and IPN are one and the same entity; and the third is that fatal MCLS and IPN are distinctive but not totally separate entities and are not mutually exclusive.

Classifications based on morphological or histopathological changes, rather than pathogenetic mechanisms, have obvious limitations. Although the pathological features of fatal MCLS and IPN are indistinguishable, these terms may not indicate an identical disease process and the conditions may not have the same cause.

Fig 2.—Relationship between fatal mucocutaneous lymph node syndrome (MCLS) and infantile periarteritis nodosa (IPN). Fatal MCLS and IPN are separate and distinct entities that are mutually exclusive (left). Fatal MCLS and IPN are one and the same entity (center). Fatal MCLS and IPN are distinct but not separate entities that are not mutually exclusive (right).



Thus, from a pathological viewpoint, the data would merely suggest that fatal MCLS and IPN are closely related.

DIFFERENTIAL DIAGNOSIS

Clinical Picture

The clinical picture of MCLS is striking, but other infectious and noninfectious illnesses have similar features. Among these are staphylococcal scarlet fever, erythema multiforme minor, leptospirosis, and IPN. Others include erythema multiforme exudativum (Stevens-Johnson syndrome), streptococcal scarlet fever, toxic shock syndrome, rat-bite fever, tick typhus (Rocky Mountain spotted fever), rubella, rubeola, primary Epstein-Barr virus infection, enteroviral infections, roseola infantum, toxoplasmosis, juvenile rheumatoid arthritis, systemic lupus erythematosus, Reiter's syndrome, Behçet's disease, drug eruption with fever, and acrodynia.

Kawasaki realized that several diseases shared clinical features with MCLS, but he thought that the similarities were more apparent than real. He attempted to enumerate the distinctive findings of Stevens-Johnson syndrome, scarlet fever, acrodynia,[23,90] and MCLS. The differential clinical features of MCLS and other mucocutaneous disorders are shown in the Table.

Care must be exercised in the diagnostic evaluation of patients with acute febrile illnesses characterized by prominent mucocutaneous features. Fortunately, if close attention is given to detail, most of these conditions are easily distinguished from MCLS.

Reiter's syndrome[91] is rare in childhood and unreported in infancy. Prolonged fever, conjunctival hyperemia, evanescent erythematous rash, dysuria, and arthralgia or arthritis are typically present. Keratodermia blennorrhagia may be seen occasionally. Changes of the lips, the oropharyngeal cavity, and the peripheral extremities are conspicuously absent.

Travel to an endemic area, history of tick exposure, splenomegaly, and petechial rash are helpful distinguishing differences between tick typhus and MCLS. Although titer rises to *Proteus* OX-19 and OX-K may occur in both conditions,[63,64] complement fixation antibodies to *Rickettsia rickettsiae* are lacking in patients with MCLS.

Fever, conjunctivitis, and exanthem may be manifestations of several viral illnesses, including rubeola, rubella, Colorado tick fever, and enteroviral and adenoviral infections. Changes of the lips and peripheral extremities, however, are not known to occur in these illnesses.

Clinically, scarlet fever, caused by either group A *Streptococcus* or phage-group II *Staphylococcus aureus*, resembles MCLS, but there are important differences: the lips are not red, dry, or fissured; there is no erythema or indurative edema of the hands and feet; the febrile course is usually not prolonged. The diagnosis can be confirmed by recovery of the causative organism.

The toxic shock syndrome[92] primarily affects older children and adolescents. Typically, there is fever, a toxic appearance, generalized erythroderma, swelling of the hands and feet, conjunctival suffusion with possible progression to scleral hemorrhage, hypotension, hepatic and renal abnormalities, and in the more severe cases, disseminated intravascular coagulation. Focal infection with phage-group I *Sta aureus* is detected commonly with vaginitis prominent in females.

The clinical features of leptospirosis in childhood have been reviewed recently.[93] It is usually a mild, anicteric biphasic illness, but occasionally it may be an acute systemic disease with icteric hepatitis, renal involvement, shock, and evidence of extensive vasculitis. Fever, headache, myalgia, hyperemia of the ocular conjunctivae, and an erythematous maculopapular, petechial, or purpuric rash are fre-

Clinical Features of Mucocutaneo

	MCLS	Infantile Polyarteritis Nodosa	Erythema Multiforme Minor
Age, yr	Usually < 5	Usually < 1	All ages
Fever	Prolonged	Prolonged	Prolonged
Eyes	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae; palpebral edema
Lips	Red, dry, fissured	Red	Erosions; ulcerations
Oral cavity	Diffuse erythema; "strawberry tongue"	Diffuse erythema	Erosions, aphthous-like ulcerations
Peripheral extremities	Erythema of palms and soles; indurative edema; periungal desquamation	Erythema of palms and soles; swelling of hands and feet; dry gangrene (rare)	No change
Exanthem	Erythematous, polymorphous	Erythematous, polymorphous	Erythematous, polymorphous; iris lesions
Cervical lymph nodes	Nonpurulent swelling; unilateral (frequent)	Nonpurulent swelling (frequent)	No change
Other	Meatitis; diarrhea; arthralgia and arthritis; meningitis; rhinorrhea (uncommon); ECG changes	Rhinorrhea and cough (common); diarrhea; ECG changes	Malaise; rhinorrhea; arthralgia; recurrent episodes

quent findings. Animal contact, especially dogs, cattle, swine, and rodents, is common. The diagnosis can be established by the isolation of leptospires from blood, CSF, or urine, by the detection of leptospires on dark field examination of urine, or by the demonstration of a fourfold or greater titer rise in leptospiral agglutinins.

The term erythema multiforme signifies a spectrum of disease ranging from a relatively mild illness referred to as erythema multiforme minor[94] to a severe, potentially life-threatening condition known as erythema multiforme exudativum or Stevens-Johnson syndrome.[95,96] At both ends of this spectrum, the collection of clinical features resembles that of MCLS. Differences are sufficiently discrete to differentiate MCLS from most cases of erythema multiforme exudativum,[95,96] which is characterized by extensive bullae formation, followed by erosion and a grayish-white pseudomembrane of the oral mucous membranes; ulcerations of other mucosal surfaces (eg, genital, anal, esophageal, tracheal); severe catarrhal conjunctivitis and chemosis with progression in some cases to uveitis, corneal ulcerations, iritis, or panophthalmitis; an erythematous polymorphous exanthem with vesicles, bullae, and extensive exfoliation.

The differences in clinical features between MCLS and erythema multiforme minor are less pronounced. Features common to both are prolonged fever, rash, conjunctival involvement, and changes of the lips and oral cavity. The conjunctival hyperemia and exanthem may be virtually indistinguishable. Whereas the characteristic cutaneous lesion of erythema multiforme minor is the iris or target lesion, this may be absent; instead there may be an erythematous polymorphous rash of symmetrical distribution involving the palms and soles and the extensor surfaces of extremities, particularly the dorsal aspects of the hands and feet. The mucosal lesions of erythema multiforme minor unlike those of MCLS consist of erosions and aphthous-like ulcerations of the lips and oral cavity. Indurative edema of the hands and feet, periungal desquamation, and cardiac or coronary artery involvement have not been described in erythema multiforme minor.

Usually MCLS can be differentiated from other mucocutaneous syndromes on clinical grounds alone. The possible exception to this is IPN, a disease of unknown origin and of nearly uniform fatality.[86-88,97,98] Retrospective tabulation of the clinical findings of IPN[86-88] indicates that a relatively constant clinical complex exists that is not unlike MCLS. The

h Node Syndrome (MLNS) and Other Mucocutaneous Syndromes

Erythema Multiforme Exudativum	Streptococcal Scarlet Fever	Staphylococcal Scarlet Fever	Toxic Shock Syndrome	Leptospirosis	Tick Typhus	Reiter's Syndrome
Usually 3-30	Usually 2-8	Usually 2-8	Usually adolescent	Usually > 2	Usually > 5	Usually > 10
Prolonged	Variable	Variable	Usually < 10 days	Variable	Usually 5-10 days	Prolonged
Catarrhal conjunctivitis; chemosis; iritis; uveitis; panophthalmitis	No change	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae; uveitis	Hyperemia of the ocular conjunctivae; palpebral edema	Hyperemia of the ocular conjunctivae; keratitis; iritis; uveitis
Erosions; crusted, fissured, bleeding	No change	No change	Red	No change	No change	No change
Erythema; bullae, ulcers, pseudomembrane formation	Pharyngitis; palatal petechiae; "strawberry tongue"	Pharyngitis	Erythema; pharyngitis	Pharyngitis	Erythema	No change
No change	Periungal membranous desquamation	No change	Swelling of the hands and feet; dry gangrene	Gangrene of the hands and feet (rare)	Swelling of the hands and feet	No change
Erythematous, polymorphous; iris lesions, vesicles, bullae, crusts	Finely papular erythroderma; Pastia's lines; circumoral pallor	Finely papular erythroderma; Pastia's lines	Erythroderma	Erythematous, maculopapular, petechial or purpuric	Maculopapular, petechial; centrifugal	Erythematous, evanescent
Nonpurulent swelling (occasional)	Nonpurulent or purulent swelling (frequent)	Nonpurulent or purulent swelling (occasional)	No change	Nonpurulent swelling (infrequent)	No change	No change
Malaise; cough, rhinorrhea, pneumonitis; vomiting; arthralgia; recurrent episodes	Malaise; vomiting		Headache; confusion; hypotension; icteric hepatitis; diarrhea; coagulopathy; renal injury	Headache; myalgia; abdominal pain; icteric hepatitis; meningitis	Headache; myalgia; photophobia; arthralgia; splenomegaly; stupor	Dysuria and urethritis; arthralgia and arthritis

principal clinical and laboratory features of IPN are persistent pyrexia, hyperemia of the ocular conjunctivae, generalized polymorphous exanthem, rhinorrhea, diarrhea, leukocytosis, and ECG changes. Other reported findings include reddened lips, diffuse erythema of the oropharyngeal mucosa, erythema of the palms and soles, swelling and rarely gangrene of the hands and feet, nonpurulent enlargement of the cervical lymph nodes, and hypertension. There are no apparent qualitative differences in the clinicopathological features of MCLS and IPN, but the majority of IPN cases do not fulfill at least five of the diagnostic criteria of MCLS.[15]

Relationship Between MCLS and Other Diseases With Mucocutaneous

A schematic representation of the clinicopathologic relationship between MCLS and other febrile illnesses with prominent mucocutaneous manifestations is shown in Fig 3. From the foregoing descriptions, MCLS and IPN do appear to be closely related. Whether MCLS represents the nonfatal form of IPN or whether IPN represents the fatal form of MCLS will probably be resolved only when the etiology and pathogenesis of these conditions are fully elucidated. In the meantime, the clinician should be aware of the clinical and pathological similarities and should diligently exclude potentially treatable, well-recognized causes of acute febrile mucocutaneous syndromes. This accomplished, and provided the diagnostic guidelines are fulfilled, the diagnosis of MCLS may be made.

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of MCLS are unknown. Some of the clinical and epidemiological features are compatible with infectious or postinfectious immunological processes or with reactions to •toxigenic substances. Presently, however, there are no prime candidates for this triggering event, and it has not been established that the interaction of several ubiquitous antigens comprises the precipitating stimulus.

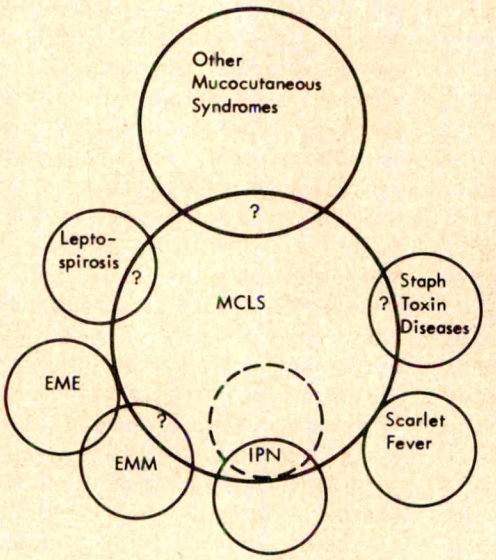


Fig 3.—Clinicopathologic relationship between mucocutaneous lymph node syndrome (MCLS) and other febrile illnesses with prominent mucocutaneous manifestations. EME indicates erythema multiforme exudativum; EMM, erythema multiforme minor; IPN, infantile polyarteritis nodosa; Staph, staphylococcal.

Infectious Agents

Microorganisms have been recovered from various specimens or detected in tissues of patients with MCLS. However, it is unclear whether these infections were concurrent with and independent from or antedated and were related causally with the development of MCLS.

Bacteria

Routine aerobic and anaerobic bacterial cultures of blood, urine, feces, CSF, pericardial fluid, lymph node aspirate, and respiratory secretions have been negative or have yielded normal flora. Serological testing for bacterial antigens, including *Salmonella O* and *H*,[21,29] *Brucella*,[21,36,56] paratyphoid A and B,[21,36] group A *Streptococcus* (streptolysin O, deoxyrinonuclease B), *Yersinia*,[29] and *Treponema pallidum*[29,63] have been uniformly negative.

Leptospires have been suggested as being etiologically involved in MCLS.[93] While leptospirosis may possibly mimic MCLS,[99] the total absence of leptospiral agglutinins in the sera of patients with MCLS belies any causative association.‖

Phage group 1 staphylococci capable of producing a new, dermal toxin have been recovered recently from the nasopharynx of an infant with typical MCLS.[92] *Staphylococcus aureus* has been reportedly isolated from other patients with MCLS. Coronary vasculitis has been observed recently in cases of toxic shock syndrome (unpublished data, September 1980 [J.K.T.]); however, the relationship of staphylococci to MCLS remains unsubstantiated.

Rickettsia

In 1973, Hamashima et al reported the detection of rickettsia-like bodies by electron microscopy in biopsy specimens of skin and cervical lymph nodes from eight patients with MCLS.[101] These rickettsia-like bodies were located within cytoplasmic vacuoles of macrophages and were also found clustered in the vascular lumen. They were Gram-negative and appeared as pink granules with Macchiavello stain. Isolation attempts were performed by inoculating guinea pigs and mice with whole blood from patients who were in the acute stages of MCLS.[102] Homogenates of liver and spleen prepared from these animals were then serially passaged and used to inoculate the yolk sacs of embryonated hens' eggs. An organism resembling rickettsia was recovered but was

‖References 21,30,36,45,56,60,63,64,100.

lost after storage at −80 °C for two weeks.[102]

Although rickettsia-like bodies have been reported by another group of investigators,[48] other efforts to duplicate Hamashima's results have been unsuccessful. Although Weil-Felix reactions may be positive in patients with MCLS,[63,64] they are usually negative.[21,36,37,42,61,62] Specific serological tests for known rickettsial diseases have also been negative.[20,29,36,40,61,63,65] The widespread geographical distribution, lack of definite seasonal pattern, absence of known vectors, and unresponsiveness to antibiotics make it difficult to reconcile a possible rickettsial origin for MCLS.

Viruses

Parainfluenza virus type 2,[56] adenovirus type 3,[70] herpes simplex virus,[70] and echo virus type 11,[70] have been recovered from patients with MCLS. However, conventional virus isolation attempts in tissue culture of respiratory secretions, feces, urine, CSF, pericardial fluid, conjunctival scrapings, joint fluid, and tissues taken at autopsy have generally failed to yield filterable agents.¶ Moreover, serological evidence of recent viral infection has been lacking in most studied cases. Significant rises in antibody titer have been absent to adenovirus,# herpes simplex virus,[23,29,43,45,63] cytomegalovirus,[21,29,31,45,49,62] varicella-zoster virus,[45,63] Epstein-Barr virus[56] (differential absorption test [Monospot][29,30,42,60-63,65] and heterophile[27,36,49,56]), vaccinia virus,[63] poliovirus,[23] coxsackievirus,[20,29] echo virus,[20,23,49] respiratory syncytial virus,[31,63] parainfluenza virus types 1, 2, 3,[29,49,63] Sendai virus,[43,45] mumps virus,[23,45] influenza A and B viruses,[21,29,31,36,45,61,63] rubeola virus,** rubella virus,[20,21,29,31,62,63,65] Colorado tick fever virus,[63,64] lymphocytic choriomeningitis virus,[29] reovirus types 1, 2, 3,[49] and hepatitis B virus.[36,53,56]

Serological testing and isolation techniques, however, have been far from exhaustive. Slowly replicating or noncultivable viruses could be involved. Additional unsuccessful attempts at virus isolation by inoculating a variety of cell lines and experimental animals, including guinea pigs, mice, and infant primates, and attempts at detecting filterable agents by immune electron microscopy have been reported recently by Melish et al,[78] but further attempts need to be made before a viral cause can be definitely excluded.

Others

There have been less-intensive searches for mycoplasmal organisms, protozoa, fungi, and chlamydial organisms. The few available isolation attempts and serological studies for these agents have been negative: cold agglutinins,[23,49,56,65] *M pneumoniae*,†† chlamydial psittacosis-lymphogranuloma-venereum,[21,29,36,45,63,64] *Toxoplasma gondii*.[20,29,36,43,56]

Toxigenic and Pharmacologically Active Substances

The relative absence of case clustering in MCLS is quite unlike patterns of illnesses caused by known environmental toxins. However, similarities in clinical findings between acrodynia and MCLS[90] have prompted examinations of biological specimens for heavy metals. Hair and serum mercury levels[21,54,90,103] have not been elevated in patients with MCLS. Serum lead levels have also been normal.[21]

Environmental pollutants or commonly used drugs and other chemicals may be pathogenetically involved, but none has been identified to date.[103]

Immunological Process

The significance of the nearly epidemic incidence of MCLS in Japan and of the disproportionate number of cases in children of Japanese ancestry in Hawaii is uncertain. Several human diseases are known to occur more frequently in genetically susceptible individuals as defined by specific histocompatibility antigens (HLA).[104,105] An association between HLA phenotypes and MCLS could not be shown by Matsuda et al[106] or by Melish et al.[78] Recently, however, in a much larger study comparing the HLA profiles of 205 unrelated Japanese children with MCLS with those of 500 normal, healthy unrelated control subjects, Kato et al[107] demonstrated that the frequency of HLA-Bw22 was significantly greater in the former group. Moreover, when HLA-Bw22J2, a subtype of Bw22 reportedly found only in Japanese, was examined, it was found even more commonly in patients with MCLS. The incidence of HLA-Bw22 is higher among Japanese than among Caucasians, and this antigen is virtually absent in some ethnic groups.[107]

While multiple factors are likely to be involved in the pathogenesis of MCLS, the usual manifestations of this disease seem more likely to develop in children genetically programmed for a specific immune response to certain as yet unidentified stimuli. Evidence for mechanisms involving immune-complex deposition or cellular- and/or humoral-mediated immunological injury in MCLS is scanty and in some instances contradictory.

Humoral Response

B-cell numbers,[54,108] proliferative responses to lipopolysaccharide,[108] and quantitative serum immunoglobulin levels[21,49,56,61,62] are generally normal for age. Elevation in levels of IgG,[63] IgA,[63] IgM,[24,29,63] and IgE[54,65,109] have been reported sporadically. Of these, IgE has received the most attention, primarily because increased levels have been found in two patients with IPN.[110] The role, if any, of IgE in the development of vasculitis in MCLS remains obscure, but it may act by promoting increased vascular permeability and subsequent antigen-antibody deposition and leukocyte migration.[44,109]

Tests for autoimmune phenomena, including antinuclear antibodies, lupus erythematosus cell preparations, rheumatoid factor, and antitissue antibodies, have been negative.

Total hemolytic complement (CH_{50}) are early components of complement (C3, C4, C5) have been examined by few investigators. The data are somewhat confusing because the temporal relationship of these determinations to the stage of illness is not usually

¶ References 21,24,28,30,32,52,53,62,63,65.
# References 21,23,29,31,45,49,61-63.
** References 20,21,29,31,43,45,62,63.

†† References 1,20,29,31,36,56,62,63.

stated. Levels of CH_{50},[30,54,56] C3,[43,54,62] C4,[43,54] and C5,[54] however, have been normal or elevated except in a few instances: in one well-studied case, Fossard and Thompson[44] reported depressed levels of CH_{50}, C3 and C4 during the acute phase (day 12) and elevated levels during recovery (day 40); transient depression of C3 during the seventh day of illness was reported by Melish et al[21] in one of four MCLS cases studied.

Circulating immune complexes have been detected rarely.[44,54,108] Whether actual deposition of such complexes occurs is unclear.

Cell-Mediated Response

T-cell numbers have been normal in the few cases studied to date.[54,108] Lymphocyte transformation with phytohemagglutinin has been normal,[108] but in mixed lymphocyte culture reactions, suppression of monocyte function has been reported during the acute phase of illness.[108]

Phagocytic Function

Peripheral neutrophils from patients with MCLS appear to have no defect in phagocytic capability or intracellular killing as determined by reduction of nitro blue tetrazolium.[54,111] Amplification of nitro blue tetrazolium reduction has been observed following the activation of neutrophils with *Proteus* OX-2 antigen.[111]

TREATMENT

Presently there is no accepted treatment for MCLS. Various treatment regimens have been tried on an empirical basis. The issues regarding therapy are several, but tend to be conditional because of insufficient knowledge about the etiology and pathogenesis of the disease process: (1) If an infectious agent is involved in the pathogenesis of MCLS, what role, if any, does antimicrobial chemotherapy have? (2) If the vasculitis of MCLS is the result of an overly exuberant immunological response by the host, what role, if any, do anti-inflammatory or immunosuppressive drugs have? (3) If the dreaded complication of MCLS, namely, coronary thrombosis, is due to thrombocytosis and accelerated platelet aggregation, what role, if any, do antiplatelet agents have? There is limited information on the efficacy of all treatment modalities, and additional controlled studies are needed.

Antimicrobial Agents

Nearly all infants and children with MCLS have received antibiotic therapy during the course of illness. Penicillins, cephalosporins, aminoglycosides, sulfonamides, macrolides, chloramphenicol, and tetracyclines have been prescribed. Although comparative trials have not been performed, none of these antibiotics have been associated with clinical improvement.

Antiinflammatory Drugs

Anecdotal accounts of the effectiveness of acetylsalicylic acid (aspirin)[39,54] and corticosteroids[27,44,66] in the symptomatic treatment of MCLS have appeared. However, in a controlled trial,[112] neither prednisolone (2 mg/kg/day) nor aspirin (100 mg/kg/day) seemed to affect the duration of fever or any other clinical parameter. Azathioprine was also ineffective.[112]

Recent data suggest that steroids may have a deleterious effect with regard to the development of coronary aneurysms.[113] Although the number of patients examined was too small, it appeared that the incidence of this adverse effect might be reduced if patients were also given low doses of aspirin (30 mg/kg/day).[113]

Antiplatelet Drugs

One of the stated goals of treatment of MCLS is the prevention of coronary thromboarteritis and of aneurysm formation. Prompt suppression of the accelerated platelet aggregation seen in MCLS has been achieved with aspirin and with flurbiprofen, D-L, 2-(fluoro-4-bi-phenylyl) propionic acid.[72,114] Doses of aspirin capable of reducing platelet aggregation have not altered the incidence of coronary aneurysms in patients with MCLS so treated, but may be effective in the prevention of sudden death due to coronary thrombosis.[113] Prolonged treatment with low doses of aspirin has been recommended by Kato et al[113] and T. Kawasaki, MD (verbal communication, 1979).

CONCLUSION

Although there appears to be considerable overlap between MCLS and other acute illnesses with prominent mucocutaneous manifestations, the six cardinal criteria do seem to define a distinct clinical entity. That is, there seems to be a definable group of infants and children whose clinical illnesses more closely resemble the original descriptions by Kawasaki than other previously well-described infectious or noninfectious diseases. However, this particular group may well be quite heterogeneous with regard to precipitating events.

As with other recently described diseases and syndromes, reasonable doubt and controversy continues to surround this elusive malady. The clinical and pathological features of MCLS and IPN are virtually indistinguishable, but their precise relationship remains to be defined. Like IPN[115] hypersensitivity has been speculated as being pathogenetically involved, but the dearth of immunopathological data does not permit definite conclusions.

Much remains to be learned about the etiology and pathogenetic mechanisms of MCLS. Until such time that a clearer understanding is available, the designation acute febrile mucocutaneous lymph node syndrome, which has been adopted by the World Health Organization, seems appropriate.

References

1. Kawasaki T: Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children: Clinical observations of 50 cases (in Japanese). *Jpn J Allergol* 16:178-222, 1967.
2. Fetterman GH, Hashida Y: Mucocutaneous lymph node syndrome (MLNS): A disease widespread in Japan which demands our attention. *Pediatrics* 54:268-270, 1974.
3. Hussey HH: Mucocutaneous lymph node syndrome. *JAMA* 236:292, 1976.
4. Riley HD: Mucocutaneous lymph node syndrome (Kawasaki disease). *J Infect Dis* 134:302-305, 1976.
5. Kawasaki disease. *Lancet* 1:675-676, 1976.
6. Mucocutaneous lymph node syndrome: A new disease. *Br Med J* 1:407, 1977.
7. Hammond BL: Mucocutaneous lymph node syndrome. *Ohio State Med J* 73:612-616, 1977.
8. Kahn G: Mucocutaneous lymph node syndrome (Kawasaki's disease). *Arch Dermatol* 114:948-950, 1978.

9. Morens DM, Nahmias AJ: Kawasaki disease: A 'new' pediatric enigma. *Hosp Pract* 13:109-112, 119-120, 1978.

10. Terezhalmy GT: Mucocutaneous lymph node syndrome: Review of a recently described disease complex. *Oral Surg* 47:26-30, 1979.

11. Kawasaki T, Kusakawa S, Shigematsu I (eds): *Progress of Research on Kawasaki Disease (MCLS).* Tokyo, Kindai Shuppan Co, 1976.

12. Shiokawa Y (ed): *Vascular Lesions of Collagen Diseases and Related Conditions.* Tokyo, University of Tokyo Press, 1977.

13. Becker AE: Kawasaki disease. *Lancet* 1:864, 1976.

14. Becker AE: Mucocutaneous lymph node syndrome or infantile polyarteritis nodosa? *Pediatrics* 60:774, 1977.

15. Landing BH, Larson EJ: Are infantile periarteritis nodosa with coronary artery involvement and fatal mucocutaneous lymph node syndrome the same?: Comparison of 20 patients from North America with patients from Hawaii and Japan. *Pediatrics* 59:651-662, 1977.

16. Aterman K: A possible early example of mucocutaneous lymph node syndrome. *J Pediatr* 92:1027-1028, 1978.

17. Kato H, Koike S, Sasaguri Y: Clinicopathological studies of diseases associated with vasculitis: Kawasaki disease (MCLS) and infantile polyarteritis nodosa (in Japanese). *Nippon Rinsho* 36:753-767, 1978.

18. Yanagawa H: Epidemiology of Kawasaki disease (in Japanese). *Jpn J Clin Med* 34:275-283, 1976.

19. Morens DM, O'Brien RJ: Kawasaki disease in the United States. *J Infect Dis* 137:91-93, 1978.

20. Brown JS, Billmeier GJ Jr, Cox F, et al: Mucocutaneous lymph node syndrome in the continental United States. *J Pediatr* 88:81-83, 1976.

21. Melish ME, Hicks RM, Larson EJ: Mucocutaneous lymph node syndrome in the United States. *Am J Dis Child* 130:599-607, 1976.

22. Bitter JJ, Friedman SA, Paltzik RL, et al: Kawasaki's disease appearing as erythema multiforme. *Arch Dermatol* 115:71-72, 1979.

23. Kawasaki T, Kosaki F, Okawa S, et al: A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 54:271-276, 1974.

24. Lauer BA, Bruhn FW, Todd JK, et al: Mucocutaneous lymph node syndrome in Denver. *Am J Dis Child* 130:610-612, 1976.

25. Robinson R, Adler R: Mucocutaneous lymph node syndrome in California. *J Pediatr* 88:1069-1070, 1976.

26. Taneja A, Saxena U: Mucocutaneous lymph node syndrome: Case report. *Indian Pediatr* 14:927-931, 1977.

27. Majeed HA, Olson IA: Kawasaki disease in Kuwait: A report of two cases. *Acta Paediatr Scand* 67:525-528, 1978.

28. Nyerges G, Barna M, Molnar L: Mucocutaneous lymph node syndrome: Three cases observed in Hungary. *Acta Paediatr Acad Sci Hung* 19:1-7, 1978.

29. Goldsmith RW, Gribetz D, Strauss L: Mucocutaneous lymph node syndrome (MLNS) in the continental United States. *Pediatrics* 57:431-435, 1976.

30. Magilavy DB, Speert DP, Silver TM, et al: Mucocutaneous lymph node syndrome: Report of two cases complicated by gallbladder hydrops and diagnosed by ultrasound. *Pediatrics* 61:699-702, 1978.

31. Bernhardt IB: Mucocutaneous lymph node syndrome with encephalopathy in the continental United States. *West J Med* 125:230-233, 1976.

32. Cook A, L'Heureux P: Radiographic findings in the mucocutaneous lymph node syndrome. *Am J Roentgenol* 132:107-109, 1979.

33. Tanaka N: Kawasaki disease (acute febrile infantile mucocutaneous lymph node syndrome) in Japan: Relationship with infantile periarteritis nodosa. *Pathol Microbiol* 43:204-218, 1975.

34. Tanaka N, Sekimoto K, Naoe S: Kawasaki disease: Relationship with infantile periarteritis nodosa. *Arch Pathol Lab Med* 100:81-86, 1976.

35. Wentworth P, Silver MD: Fatal mucocutaneous lymph node syndrome in Canada? *Can Med Assoc J* 115:299-305, 1976.

36. Kegel SM, Dorsey TJ, Rowen M, et al: Cardiac death in mucocutaneous lymph node syndrome. *Am J Cardiol* 40:282-286, 1977.

37. Kim J, Yeo Y, Lee DB: Mucocutaneous lymph node syndrome: Clinical observations of eight cases (in Korean). *Korea N Med J* 16:1157-1160, 1973.

38. Melish ME, Hicks RM, Larson EJ: Mucocutaneous lymph node syndrome (MCLS) in the US, abstracted. *Pediatr Res* 8:427, 1974.

39. Russell AS, Zaragoza AJ, Shea R: Mucocutaneous lymph node syndrome in Canada. *Can Med Assoc J* 112:1210-1211, 1975.

40. Radford DJ, Sondheimer HM, Williams GJ, et al: Mucocutaneous lymph node syndrome with coronary artery aneurysm. *Am J Dis Child* 130:596-598, 1976.

41. Fanconi A, Bodmer P, Egloff B: Akutes mukokutanes lymph knoten syndrom (Kawasaki syndrom) mit letaler periarteriitis nodosa der kranzarterien. *Helv Paediatr Acta* 33:135-140, 1978.

42. Stephenson SR: Kawasaki disease in Europe. *Lancet* 1:373-374, 1977.

43. Lyen KR, Brook CGD: Mucocutaneous lymph node syndrome in two siblings. *Br Med J* 1:1187, 1978.

44. Fossard C, Thompson RA: Mucocutaneous lymph node syndrome (Kawasaki disease): Probable soluble complex disorder. *Br Med J* 1:883, 1977.

45. Hewitt CJ: Case of Kawasaki disease. *Br Med J* 1:883-884, 1977.

46. Scopes JW, Hulse JA: Mucocutaneous lymph node syndrome. *Br Med J* 1:511, 1977.

47. Morgan GJ, Lynch MA: Kawasaki disease in Canterbury. *Arch Dis Child* 53:916-917, 1978.

48. Carter RF, Haynes ME, Morton J: Rickettsia-like bodies and splenitis in Kawasaki disease. *Lancet* 2:1254-1255, 1976.

49. Della-Porta G, Alberti A: Kawasaki disease in Europe. *Lancet* 1:797-798, 1977.

50. Valaes T: Mucocutaneous lymph node syndrome (MLNS) in Athens, Greece. *Pediatrics* 55:295, 1975.

51. Ahlström H, Lundström N-R, Mortensson W, et al: Infantile periarteritis nodosa or mucocutaneous lymph node syndrome. *Acta Paediatr Scand* 66:193-198, 1977.

52. Hicsönmez G, Kanra G, Kocak H, et al: Acute febrile mucocutaneous lymph node syndrome. *Clin Pediatr* 16:480-481, 1977.

53. Smith AD: Infantile polyarteritis and Kawasaki disease. *Acta Paediatr Scand* 66:381-384, 1977.

54. Corbeel L, Delmotte B, Standaert L, et al: Kawasaki disease in Europe. *Lancet* 1:797, 1977.

55. Piette N, Carton D, Hooft C: A case of mucocutaneous lymph node syndrome. *Acta Paediatr Belg* 30:243-246, 1977.

56. Keim DE, Keller EW, Hirsch MS: Mucocutaneous lymph node syndrome and parainfluenza 2 virus infection. *Lancet* 2:303, 1977.

57. Kovacevic M, Gardner HG: Thrombocytosis associated with the mucocutaneous lymph node syndrome. *J Pediatr* 89:688, 1976.

58. Dennis MK, Ayoub EM, Graham T, et al: Mucocutaneous lymph node syndrome in Florida. *J Fla Med Assoc* 64:21-26, 1977.

59. Darby CP, Kyong CU: Mucocutaneous lymph node syndrome. *JAMA* 236:2295-2297, 1976.

60. Gross CW, Chamberlain M: Mucocutaneous lymph node syndrome: A new clinical entity. *Laryngoscope* 87:1702-1704, 1977.

61. Miriovsky M, Downing JS: Mucocutaneous lymph node syndrome. *Am Fam Physician* 17:154-157, 1978.

62. John TJ, DeBenedetti CD, Zee ML: Mucocutaneous lymph node syndrome in Arizona. *Am J Dis Child* 130:613-614, 1976.

63. Bergeson PS, Schoenike SL: Mucocutaneous lymph node syndrome: A case masquerading as Rocky Mountain spotted fever. *JAMA* 237:2299-2302, 1977.

64. Bergeson PS, Serlin SP, Corman LI: Mucocutaneous lymph node syndrome with positive Weil-Felix reaction but negative leptospira studies. *Lancet* 1:720-721, 1978.

65. Siegel CJ, Wenner HA: The mucocutaneous lymph node syndrome: Description of an affected 21-month-old child in Kansas City. *Clin Pediatr* 15:1105-1106, 1976.

66. Walker SH, Quintero BA, Heldrich FJ: Mucocutaneous lymph node syndrome. *Am J Dis Child* 130:1164, 1976.

67. Withers EH, Long WR, Lynch JB: Mucocutaneous lymph node syndrome: An additional case. *J Tenn Med Assoc* 70:731, 1977.

68. Yanagawa H, Shigematsu I: Epidemiological aspects of Kawasaki disease, in Shiokawa Y (ed): *Vascular Lesions of Collagen Diseases and Related Conditions.* Tokyo, University of Tokyo Press, 1977, pp 287-295.

69. Tominaga M, Ohshima K, Yanagawa Y, et al: An epidemic analysis of family cases of mucocutaneous lymph node syndrome (in Japanese). *Pediatr Japan* 18:59-63, 1977.

70. Kitayama T: Infectious disease theory of Kawasaki disease with special reference to the theory of virus infection as a triggering factor (in Japanese). *Jpn J Clin Med* 34:295-297, 1976.

71. Onouchi Z, Tomizawa N, Goto M, et al: Cardiac involvement and prognosis in acute mucocutaneous lymph node syndrome. *Chest* 68:297-301, 1975.

72. Yamada K, Fukumoto T, Shinkai A, et al: The platelet functions in acute febrile mucocutaneous lymph node syndrome and a trial of prevention for thrombosis by antiplatelet agent. *Nippon Ketsueki Gakkai Zasshi* 41:791-802, 1978.

73. Kato H, Koike S, Yamamoto M, et al: Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *J Pediatr* 86:892-898, 1975.

74. Hosaki J, Abe S, Yoshimatsu A, et al: Observations of coronary arterial lesions in acute febrile mucocutaneous lymph node syndrome (MCLS). *Acta Paediatr Jpn* 18:8-17, 1976.

75. Kitamura S, Kawashima Y, Kawachi K, et al: Left ventricular function in patients with coronary arteritis due to acute febrile mucocutaneous lymph node syndrome or related diseases. *Am J Cardiol* 40:156-164, 1977.

76. Kusakawa S, Asai T: Cardiovascular lesions in Kawasaki disease, in Shiokawa Y (ed): *Vascular Lesions of Collagen Diseases and Related Conditions.* Tokyo, University of Tokyo Press, 1977, pp 273-280.

77. Kato H: Natural history of Kawasaki disease, in Shiokawa Y (ed): *Vascular Lesions of Collagen Diseases and Related Conditions.* Tokyo, University of Tokyo Press, 1977, pp 281-286.

78. Melish ME, Hicks RM, Dean AG: Kawasaki Syndrome in Hawaii, abstracted. *Pediatr Res* 13:451, 1979.

79. Tomisawa M, Onouchi Z, Goto M, et al: Ultrastructure of the myocardium in acute febrile mucocutaneous lymph node syndrome. *Jpn Circ J* 41:151-157, 1977.

80. Kawasaki T: Acute febrile mucocutaneous lymph node syndrome and sudden death (in Japanese). *Acta Paediatr Jpn* 75:433-434, 1971.
81. Tanaka N, Naoe A, Kawasaki T: Pathological study on autopsy cases of MCLS (in Japanese). *J Jpn Red Cross Center Hosp* 2:85-94, 1971.
82. Yanagisawa M, Kobayashi N, Matsuya S: Myocardial infarction due to coronary thromboarteritis following acute febrile mucocutaneous lymph node syndrome (MLNS) in an infant. *Pediatrics* 54:227-281, 1974.
83. Fujiwara H, Hamashima Y: Pathology of the heart in Kawasaki disease. *Pediatrics* 61:100-107, 1978.
84. Hamashima Y, Tasaka K, Hirose S: Etiological studies of Kawasaki disease: Infectious disease theory (in Japanese). *Jpn Clin Med* 34:290-294, 1976.
85. Hirose S, Hamashima Y: Morphological observations on the vasculitis in the mucocutaneous lymph node syndrome. *Eur J Pediatr* 129:17-27, 1978.
86. Munro-Faure H: Necrotizing arteritis of the coronary vessels in infancy. *Pediatrics* 23:914-926, 1959.
87. Roberts FB, Fetterman GH: Polyarteritis nodosa in infancy. *J Pediatr* 63:519-529, 1963.
88. Benyo RB, Perrin EV: Periarteritis nodosa in infancy. *Am J Dis Child* 116:539-544, 1968.
89. Chamberlin JL III, Perry LW: Infantile periarteritis nodosa with coronary and brachial aneurysms: A case diagnosed during life. *J Pediatr* 78:1039-1042, 1971.
90. Cheek DB: Common on mucocutaneous lymph node syndrome: Could it be a heavy metal poisoning? *Pediatrics* 56:335-337, 1975.
91. Lockie GN, Hunde GG: Reiter's syndrome in children. *Arthritis Rheum* 14:767-772, 1971.
92. Todd J, Fishaut M, Kapral F, et al: Toxic-shock syndrome with phage-group I staphylococci. *Lancet* 2:1116-1118, 1978.
93. Wong ML, Kaplan S, Dunkle LM, et al: Leptospirosis: A childhood disease. *J Pediatr* 90:532-537, 1977.
94. Chanda JJ, Callen JP: Erythema multiforme and the Stevens-Johnson syndrome. *South Med J* 71:566-570, 1978.
95. Stevens AM, Johnson FC: A new eruptive fever associated with stomatitis and ophthalmia: Report of two cases in children. *Am J Dis Child* 24:526-533, 1922.
96. Bukantz SC: The Stevens-Johnson syndrome. *DM* 1-36, 1968.
97. Tang PHL, Segal AJ: Polyarteritis nodosa of infancy: Fatal late complication. *JAMA* 217:1666-1670, 1971.
98. Crouch JA, Diehl AM: Cardiac complications: Periarteritis nodosa of infancy. *J Kans Med Soc* 74:78-81, 108, 1973.
99. Humphry T, Sanders S, Stadius M: Leptospirosis mimicking MLNS. *J Pediatr* 91:853, 1977.
100. Ohtaki C, Tomiyama T, Suzuki M, et al: Leptospiral antibody and MLNS. *J Pediatr* 93:896, 1978.
101. Hamashima Y, Kishi K, Tasaka K: Rickettsia-like bodies in infantile acute febrile mucocutaneous lymph node syndrome, *Lancet* 2:42, 1973.
102. Tasaka K, Hamashima Y: Studies on rickettsia-like body in Kawasaki disease: Attempts at the isolation and characterization. *Acta Pathol Jpn* 28:235-245, 1978.
103. Takabatake E: Etiological studies of Kawasaki disease: A toxicological theory (in Japanese). *Jpn J Clin Med* 34:302-305, 1976.
104. Svejgaard A, Platz P, Ryder LP, et al: HL-A and disease associations: A survey. *Transplant Rev* 22:3-43, 1975.
105. Bach FH, van Rood JJ: The major histocompatibility complex: Genetics and biology. *N Engl J Med* 295:927-936, 1976.
106. Matsuda I, Hattori S, Nagata N, et al: HLA antigens in mucocutaneous lymph node syndrome. *Am J Dis Child* 131:1417-1418, 1977.
107. Kato S, Kimura M, Tsuji K, et al: HLA antigens in Kawasaki disease. *Pediatrics* 61:252-255, 1978.
108. Yata J, Nakagawa T, Sawa E: Some immunological studies on Kawasaki disease, in Shiokawa Y (ed): *Vascular Lesions of Collagen Diseases and Related Conditions*. Tokyo, University of Tokyo Press, 1977, pp 335-336.
109. Kusakawa S, Heiner DC: Elevated levels of immunoglobulin E in the acute febrile mucocutaneous lymph node syndrome. *Pediatr Res* 10:108-111, 1976.
110. Krous HF, Clausen CR, Ray CG: Elevated immunoglobulin E in infantile polyarteritis nodosa. *J Pediatr* 84:841-845, 1974.
111. Tasaka K, Hamashima Y: Function of phagocytosis and intracellular killing of peripheral neutrophils in Kawasaki disease. *Acta Pathol Jpn* 28:247-252, 1978.
112. Kusakawa S: Treatment of Kawasaki disease (in Japanese). *Jpn J Clin Med* 34:306-310, 1976.
113. Kato H, Koike S, Yokoyama T: Kawasaki disease: Effect of treatment on coronary artery involvement. *Pediatrics* 63:175-179, 1979.
114. Nishizawa EE, Wynalda DR, Suydam DR, et al: Flurbiprofen, a new potent inhibitor of platelet aggregation. *Thromb Res* 3:577-588, 1973.
115. Rich AR, Gregory JE: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull Hopkins Hosp* 72:65-88, 1943.

60 Years Ago in the AJDC

The Bacillus of Pfeiffer in Inflammations of the Respiratory Tract in Children

Studying the role of the bacillus of Pfeiffer in respiratory ailments, 1,000 sputum cultures were examined in the first three months of 1920. These cultures were taken by cough swabs from a variety of patients with pneumonia, other respiratory tract disease, measles, and a group of controls. Seventy per cent. of the entire group were under the age of 13 years, the rest were over 20 years of age. Results by categorical diagnosis were:

	% positive
101 Pneumonia patients	74
122 Other febrile respiratory disease	85
473 Simple colds	55
15 Tuberculosis	33
23 Measles	60
266 Controls	10

The authors comment that the prevalence of the bacillus of Pfeiffer was greater at that time than during an earlier period of 1909-10 when there was no influenza present in the population. They observed that its presence can frequently be traced to contact with someone sick with respiratory tract disease and conjectured that it may be "an early secondary invader whose presence modified the clinical and pathological picture."

Martha Wollstein, MD, Ralph C. Spence, MD, Babies' Hospital, New York (19:459, June 1920).

Special Feature

Radiological Case of the Month

Lionel W. Young, MD; Contributed by Mutsuhisa Fujioka, MD

Clinical History.—This 13-month-old baby boy was admitted to Children's Hospital of Pittsburgh because of wheezing of two days' duration. A chest roentgenogram was obtained (Fig 1). He had had meningitis at 3 months of age and recurrent otitis media and recurrent episodes of respiratory tract infection. He had been admitted to another hospital one month previously with a temperature of 42 °C and right upper-lobe pneumonia. The infant received antibiotics, his condition improved, and he was discharged home although he continued to have midanterior chest wall retractions.

On physical examination, his respirations were 40/min; pulse rate, 160 beats per minute; and temperature, 38.2 °C. He was in moderate respiratory distress, and midanterior chest wall retraction was noted. On auscultation, he had prolonged expiration with diffuse wheezing and bilateral rhonchi. Right bronchoscopy yielded purulent material and was followed by a right bronchogram (Fig 2).

From the Department of Radiology, Children's Hospital of Pittsburgh.

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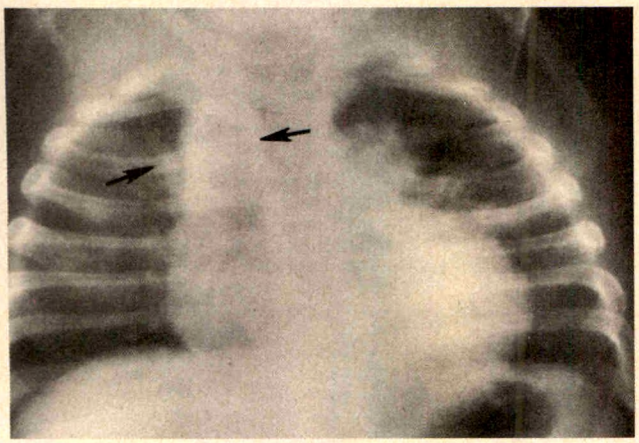

Figure 1.

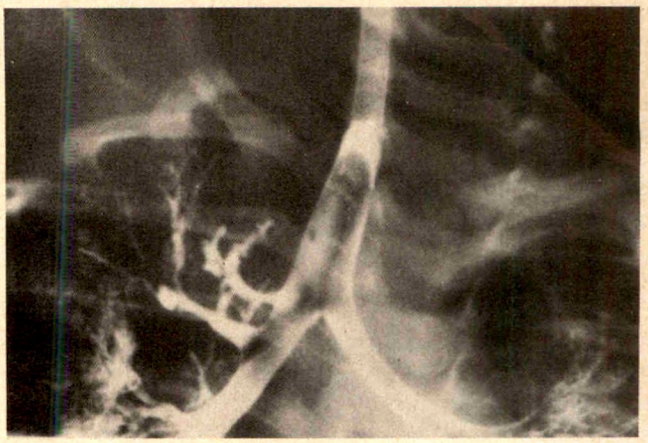

Figure 2.

Denouement and Discussion

Fig 1.—Posteroanterior roentgenogram shows area of increased density in medial portion of right upper lobe consistent with apical atelectasis and/or pneumonia.

Fig 2.—Bronchogram shows anomalous apical bronchus arising at tracheobronchial junction on right. Bronchi are irregular in shape and in distribution due to chronic inflammation.

Anomalous Apical Bronchus of the Right Upper Lobe

Anomalous bronchi of the right upper lobe are uncommon but relatively well recognized. Le Roux[1] found anomalous right upper bronchi in 30 (3%) of 1,000 bronchograms. Of special interest is their wide anatomical variation. Specifically, if a bronchus arises directly from the trachea, it is called a "tracheal bronchus." The tracheal bronchus may be a small rudimentary bronchus, a form of tracheal diverticulum,[2] or it may be the bronchus to the right upper lobe originating from the trachea.[3] A tracheal bronchus is the normal morphologic arrangement in pigs and other ruminants. Therefore, the segment of the upper lobe drained by a tracheal bronchus has been called "lobus porcinus" or "pig lobe."[4] On the other hand, an apical bronchus arising either from the right side of the trachea or from the lateral wall of the right primary bronchus before the lobar bronchi are given off is termed "pre-eparterial bronchus."[5] "Eparterial bronchus" refers to a bronchus over an artery and is the specific designation for the first branch of the normal right primary bronchus that courses over the right pulmonary artery. Variations from normal develop during periods when the segmental and subsegmental buds are being formed.[6]

In our patient, the apical bronchus of the right upper lobe arises at the junction of the trachea and the right main bronchus.

Anomalous bronchi may have no special clinical importance and they may be incidentally discovered during bronchoscopy, bronchography, or during surgery. The affected segment may be hyperinflated and take on a cystic form.[7] However, the lobe of an anomalous bronchus may also be the focus for atelectasis, and either atelectasis or cystic hyperinflation may predispose to recurrent pneumonia. Although recurrent pneumonia is often associated with pulmonary sequestration, this condition is extremely rare in upper lobes and does not have a normal bronchial tree despite having pulmonary blood supply.[8] The roentgenologic findings of a homogeneous density in the right upper lung area may be involvement of the lobe, but the finding is not specific. Loculated pleural effusion or a prominent right thymic lobe may simulate this.[9] Tomography may be helpful if anomalous bronchi are suspected and bronchoscopy and/or bronchography may be necessary to confirm the diagnosis.

Surgical resection of the affected segment is the treatment of choice in a patient with recurrent pneumonia to prevent additional episodes of pneumonia or other complications.[10] In our patient, the affected segment was resected and the patient has done well with no recurrence of upper respiratory tract infection.

References

1. Le Roux T: Anatomical abnormalities of the right upper bronchus. *J Thorac Cardiovasc Surg* 44:225-227, 1962.
2. Surprenant EL, O'Loughlin BJ: Tracheal diverticula and tracheobronchomegaly. *Dis Chest* 49:345-351, 1966.
3. Schulte-Brinkmann W: The tracheal bronchus and its clinical significance. *Z Tuberk* 117:37-50, 1961.
4. Kobler G, Ammann RW: Accessory lung arising from upper esophagus. *Respiration* 34:236-239, 1977.
5. Boyden EA: The distribution of bronchi in gross anomalies of right upper lobe. *Radiology* 58:797-807, 1952.
6. Boyden EA: Developmental anomalies of the lung. *Am J Surg* 89:79-89, 1955.
7. Siegel MJ, Shackelford GD, Francis RS, et al: Tracheal bronchus. *Pediatr Radiol* 130:353-355, 1979.
8. Sade RM, Clouse M, Ellis FH: The spectrum of pulmonary sequestration. *Ann Thorac Surg* 18:644-658, 1974.
9. Caffey J: *Pediatric X-ray Diagnosis*, ed 7. Chicago, Year Book Medical Publishers, 1978, p 395.
10. Marks C: The ectopic tracheal bronchus: Management of a child by excision and segmental pulmonary resection. *Dis Chest* 50:652-654, 1966.

The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Clinical Memoranda

Group A β-Hemolytic Streptococci Causing Pyogenic Gingival Cyst in Infancy

Localized gingival lesions in young febrile, irritable infants have recently been described, often in association with occult pneumococcal bacteremia. A review of the literature discloses eight such reported cases, many of which had concomitant ipsilateral buccal cellulitis.[1-3] This constellation of symptoms has been so typical that Yeager[3] suggested the presence of a cystic gingival lesion in a febrile infant with leukocytosis (1) should alert the clinician to the distinct possibility of concomitant pneumococcal bacteremia and (2) seems to be pathognomonic for this bacteremia. Recently, we cared for a febrile infant who had a cystic gingival lesion, mimicking a hemorrhagic preeruption dentigerous cyst, from which a pure growth of group A β-hemolytic streptococcus was obtained. The purpose of this report is to alert the pediatrician to the entity of a pyogenic gingival cyst of infancy and to stress the importance of aggressive diagnosis and antimicrobial therapy. We emphasize the multiple etiologies of these cysts, which have been reported only in infants younger than 1 year of age.

Report of a Case.—A previously well 6-month-old female infant was admitted to the hospital because of a two-day history of fever to 39.5 °C, coryza, irritability, and the recent onset of a well-localized gingival swelling. There had been no history of gross mouth trauma. The infant seemed acutely ill, with a temperature of 38.7 °C, a pulse rate of 130 beats per minute, and respiratory rate of 44/min. There was a violaceous, 1 × 1-cm, tender, fluctuant, thin cystic lesion on the left upper incisor area of the gingival ridge, associated with minimal swelling of contiguous upper lip. No underlying tooth eruption was seen or palpated. The rest of the results of the physical examination were unremarkable. The leukocyte count was 23,500/cu mm, with 57% neutrophils. The ESR was 42 mm/hr. Many Gram-positive cocci and polymorphonuclear leukocytes were seen on Gram's stain of fluid from incision and drainage of the cyst. Subsequently, group A β-hemolytic streptococci grew on culture of the drainage. No pathogen was recovered from pretreatment blood, throat, and nasopharyngeal cultures. Treatment with intramuscular penicillin G procaine caused defervescence in 24 hours, and a ten-day course of oral penicillin potassium was completed as an outpatient. On follow-up examination, the gingiva had healed completely.

Comment.—Localized pyogenic gingival lesions in febrile, irritable young infants have recently been described. To date, there have been nine cases reported in the literature.[1-4] Eight of these nine cases have been associated with pneumococcal bacteremia, and one case was due to localized infection with *Neisseria gonorrhoeae*.[4] The present case of localized gingival lesion owing to group A β-hemolytic streptococcus brings to ten the number of cases reported. All of the described patients were infants younger than 1 year of age who were febrile and irritable and often had a remarkable leukocytosis. All of the five children with gingival lesions reported by Burech et al,[1] the twins reported by Kehne et al[2] and the single case reported by Yeager[3] had concomitant ipsilateral buccal cellulitis and occult pneumococcal bacteremia. Bacteremia was not found in the infant with the gonococcal gum abscess nor in our patient.

Although the temporal relationship of these gingival lesions to pneumococcal bacteremia is apparent, the bacterial etiology of the mouth lesions in these patients remains in doubt. To date, only three of the eight reported lesions have been cultured prior to instituting antimicrobial therapy, and only one of these three yielded *Streptococcus pneumoniae* growths.[1] Unfortunately, serotyping of blood and gingival isolates was not carried out.

The relation of teething and trauma to the etiology of gingival lesions and bacteremia in this age group has yet to be proved although in older age groups, it is well known that dental manipulation can lead to bacteremia with α streptococci.[5,6] Although the group A β-hemolytic streptococcus is an infrequent cause of upper respiratory disease in infants,[7] it has been reported as a cause of a persistent watery rhinorrhea (nasopharyngitis), often with redness and crusting of the nares.[8] To our knowledge, this organism has not been previously reported as a cause of gross cystic gingival lesions in infants.

A simple hemorrhagic preeruptive dentigerous cyst should be differentiated from pyogenic gingival cysts. Both types of cysts occur in young infants. Fussiness may accompany an erupting tooth, and even fever (38.2 °C) has been reported with teething although this association is controversial.[9] The violaceous, hemorrhagic appearance of the cyst in our infant mimicked a dentigerous cyst, but the height of the fever, leukocytosis, and elevated ESR suggested a septic process. It is important for the pediatrician to appreciate the potential seriousness of cystic gingival lesions in febrile, fussy infants and to realize that any one of several pathogens (*S pneumoniae*, *N gonorrhoeae* group A streptococci) may be involved. We suggest the following steps in the approach to these cases: (1) Blood culture and leukocyte count with differential cell count should be obtained. (2) Cystic fluid for Gram's stain and culture should be obtained by aspiration or incision of the lesion. (3) The physician should evaluate the need for CSF examination and admission to the hospital. (4) The physician should start parenteral penicillin therapy pending the results of the just-mentioned studies.

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1. Burech DL, Koranyi K, Haynes RE, et al: Pneumococcal bacteremia associated with gingival lesions in infants. *Am J Dis Child* 129:1283-1284, 1975.

2. Kehne S, Rodriguiz W, Goldenberg R, et al: Gingivitis and cellulitis in diffuse pneumococcal

infection. *South Med J* 71:473-474, 1978.

3. Yeager AM: Gingival lesions in infants with pneumococcal bacteremia. *Am J Dis Child* 133:97, 1979.

4. Urban M, Hervada A: Gonococcal gum abscess in a 10-week-old infant. *Clin Pediatr* 16:43-45, 1959.

5. Elliott RH, Dunbar JM: Streptococcal bacteremia in children following dental extraction. *Arch Dis Child* 43:451-454, 1968.

6. Speck WT, Hurwitz GA, Keller GB: Transient bacteremia in pediatric patients following dental manipulation. *Am J Dis Child* 121:286-288, 1971.

7. Powers G, Goisvert P: Age as a factor in streptococcosis. *J Pediatr* 25:481-504, 1944.

8. Streptococcosis, streptococcal fever and scarlet fever, editorial. *Conn Med J* 6:118-120, 1942.

9. Nowak AJ: Pediatric dentistry: Part I. The pre-eruption and eruption periods (birth to 36 months). *J Continental Educ Pediatr* 21:11-22, 1979.

Herpes Zoster in Early Infancy

Maternal chickenpox may result in one of the following two major clinical syndromes: early onset postnatal chickenpox or intrauterine infection.[1-2] Infection in the susceptible female early in gestation may rarely lead to severely affected infants who may display multiple congenital anomalies, as described in several similar case reports.[3-5]

Dermatomal localization, the sine qua non of shingles, has been a prominent feature of some of the case reports of the severely affected neonates as well as of a few cases of isolated disease early in life. This report documents the cases of two infants who had shingles during the first few months of life after intrauterine exposure to varicella-zoster virus.

Materials and Methods.—Standard virological procedures were used for the identification and isolation of varicella-zoster virus. Levels of complement-fixing antibody to varicella-zoster virus were determined by the methodology described by Brunell and Casey.[6] Immunofluorescence antibody was determined as previously reported.[7]

Report of Cases.—CASE 1.—A 16-year-old primigravida came during the third month of pregnancy to her obstetrician with crops of lesions at various stages of evolution, including vesicles, pustules, and scabs. A clinical diagnosis of chickenpox was made. Lesion aspirates were obtained for viral isolation in tissue culture, which subsequently yielded varicella-zoster virus. The course of maternal disease was mild and persisted for six days. The otherwise uneventful pregnancy ended with premature labor and delivery at 34 weeks' gestation.

The 2,420-g, preterm male infant was normocephalic and had no detectable defects; his Apgar scores were 9 and 10 at 1 and 5 minutes of age, respectively. At 9 weeks of age, the infant was hospitalized for pneumonitis when serial serum specimens were obtained for diagnostic evaluation.

At 4 months of age, he was seen for a rash of two days' duration. Grouped vesicles were noted in the L1-2 dermatome on the left. There had been no prior rash or known exposure to chickenpox. Varicella-zoster virus was recovered from vesicular fluid. Although the child's parents refused to return for a follow-up examination, a telephone call nine days later established that the rash had already resolved.

Seroconversion to varicella-zoster virus was noted in serial serum specimens obtained from the mother during and after the chickenpox infection. Antibody was present in cord blood serum as well as in the specimens obtained from the infant at the time of hospitalization for pneumonia and onset of illness, as given in the Table.

CASE 2.—An 18-year-old primigravida had uncomplicated chickenpox during the sixth month of gestation. Chickenpox was diagnosed by the patient's obstetrician based on clinical presentation. The index case proved to be a 7-year-old sibling who was diagnosed as having chickenpox by the child's pediatrician.

A completely normal, 3,130-g male infant was born at term. At 4 months of age, he was examined for a T3-4 vesicular eruption of two days' duration. Lesion aspirates yielded varicella-zoster virus in tissue culture. The child was otherwise asymptomatic. Growth and development were appropriate for age. All lesions were completely healed when examined two weeks later. There had been no previous rash or exposure to chickenpox. A four-fold antibody response by both complement fixing and immunofluorescence was determined.

Comment.—Contrary to earlier reports that suggested high risk for the conceptus, varicella-zoster virus infections in pregnancy are apparently benign because of inherent mechanisms that protect the fetus and newborn from, or at least ameliorate, disease in the case of in utero acquisition.[1] However, these protective barriers occasionally are breached and infection of the fetus or newborn can occur.

A few cases have been recorded in which varicella-zoster virus was believed to have been transmitted in utero during middle or late gestation and followed by the birth of a normal infant in whom shingles later developed, presumably due to reactivation of virus acquired during pregnancy.[8-10] The two babies described had shingles that were confirmed by viral isolation early in life after in utero maternal chickenpox. The course of disease was benign in both infants. This report further documents one aspect of the relationship between maternal varicella and the occurrence of shingles early in life.

Serologic Response to Varicella-Zoster Virus

Patient	Date Specimen Obtained	No. of Days Before (—) or After (+) Onset of Illness	Age	Varicella-Zoster Virus Isolation	Reciprocal of Serologic Responses*	
					CF	IFA
Mother 1	9/16/77	+2	16 yr	Yes	N	N
	10/12/77	+28	. . .	No	64	512
	5/31/78	+231	. . .	No	32	256
Infant 1	3/6/78	—122	Birth	No	32	523
	5/18/78	—49	. . .	No	16	256
	7/6/78	+1	4 mo	Yes	AC	256
Infant 2	10/24/76	+2	4 mo	Yes	32	64
	11/22/76	+33	5 mo	No	128	256

*CF indicates complement-fixing antibody; IFA, immunofluorescence antibody; N, negative; and AC, anticomplementary.

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1. Meyer JD: Congenital varicella in term infants: Risk reconsidered. *J Infect Dis* 129:215-218, 1974.

2. Gershon AA: Varicella in mother and infant, in Krugman S, Gershon AA (eds): *Infections of the Fetus and Newborn: Progress in Clinical and Virological Research.* New York, Alan R. Liss Inc, 1975, vol 3, pp 79-96.

3. Srabstein JC, Morris N, Larke RPB, et al: Is there a congenital varicella syndrome? *J Pediatr* 84:239-243, 1974.

4. Dodion-Fransen J, Dekegel D, Thiry L: Congenital varicella-zoster infection related to maternal disease in early pregnancy. *Scand J Infect Dis* 5:149-153, 1973.

5. Bai PVA, John TJ: Congenital skin ulcers following varicella in late pregnancy. *J Pediatr* 94:65-68, 1979.

6. Brunell PA, Casey HL: Crude tissue culture antigen for determination of varicella-zoster complement-fixing antibody. *Public Health Rep* 79:839-942, 1964.

7. Mazur MH, Whitley RJ, Dolin R: Serum antibody levels as risk factors in the dissemination of herpes zoster. *Ann Intern Med* 139:1341-1345, 1979.

8. Lyday JH: Report of severe herpes zoster in a 13½-year-old boy whose chickenpox infection may have been acquired in utero. *Pediatrics* 50:930-931, 1972.

9. Brunell PA, Miller LH, Lovejoy F: Zoster in children. *Am J Dis Child* 115:432-437, 1968.

10. McKendrick GDW, Raychoudhury SC: Herpes zoster in childhood. *Scand J Infect Dis* 4:23-25, 1972.

Increased Amniotic Fluid α-Fetoprotein, Familial Hydrocephalus, and Renal Dysmorphology

The association of hydrocephalus and congenital renal disease as a syndrome complex is rare. Apert's, Meckel's, Robert's, and the orofaciodigital (type 1) syndromes have occasionally been reported with this combination. All of these have easily identified physical manifestations that allow syndrome identification as do trisomy 13, trisomy 18, and triploidy. In Zellweger syndrome, severe CNS defects are reported in association with renal and hepatic cysts where, apart from a distinctive facies, visible malformations may be minimal. The familial nephrotic syndromes and infantile polycystic disease of the kidneys have no characteristic external signs. This report is concerned with two brothers and a sister who had no external physical defect apart from hydrocephalus and in whom the kidneys were abnormal.

Family History.—The mother first came to our notice in 1975 when she was 36 years old. She and her husband are not related, and the family history was normal. In 1973, in the eighth month of her pregnancy, a stillborn male infant with hydrocephalus was delivered by forceps after craniotomy. No autopsy was performed. This pregnancy was complicated by deep vein thrombosis in the final trimester for which she was treated with warfarin sodium.

In 1975, in her second pregnancy, polyhydramnios developed at 32 or 33 weeks. An abdominal roentgenogram and amniography showed a hydrocephalic fetus. The amniotic fluid had an α-fetoprotein (AFP) content of 7.4 μg/mL (upper limit of normal, 2 μg/mL). Craniotomy was performed to permit vaginal delivery and an estimated 300 to 400 mL of CSF was drained. A male infant was delivered who, contrary to all expectations, survived. He weighed 3,300 g and had an estimated gestational age of 38 weeks. Apart from hydrocephalus (head circumference, 42 cm, with gross moulding) and bilateral simian creases, no other physical defects were found. The placenta weighed 850 g, slightly more than 25% of the infant's weight, but was otherwise unremarkable. Percutaneous ventriculography revealed obstructive hydrocephalus, with a block at the level of the third ventricle. A ventriculoperitoneal shunt was inserted at the age of 4 weeks.

In 1976, this mother again became pregnant; and during the 16th week, diagnostic amniocentesis was undertaken after ultrasonography. The ultrasonogram showed no abnormality, but the amniotic fluid AFP content was 780 μg/mL (upper limit of normal, 30 μg/mL). Chromosomal analysis of the cultured amniotic fluid cells showed a normal female karyotype (46XX). The pregnancy was terminated at 18 weeks by intra-amniotic instillation of prostaglandin F_{2}, and a female fetus was delivered. No gross defect was present on external examination. Skeletal roentgenographic survey was normal, but skull measurements on the roentgenograms were larger than expected from comparison with those of other fetuses of the same gestational age.

In view of the autopsy findings on this fetus, (described later), the male infant from the second pregnancy was admitted for investigation at the age of 16 months. He was asymptomatic and developmentally normal. Apart from arrested hydrocephalus (head circumference, 54.4 cm), bilateral indirect inguinal herniae, and simian creases, no external physical defects were present. Height and weight were on the 50th and the 97th percentile for his age, respectively. Severe but asymptomatic proteinuria was present, and the nephrotic syndrome was diagnosed.The BUN level was normal, the serum cholesterol level was elevated (801 mg/dL), and the serum albumin level was low (1.83 g/L). Titers for toxoplasma, Australia antigen and antibody, and cytomegalovirus were all within normal limits. Plasma and urinary amino acid patterns showed no abnormality. Intravenous pyelography and micturating cystourethrography showed no abnormalities. At the age of 18 months, a renal biopsy was performed when the herniae were repaired (see "Renal Biopsy").

Treatment with high-dosage prednisone was ineffective, and since then, the intermittent edema has been controlled by diuretic therapy. Severe eruptive xanthomata virtually resolved on dietary therapy.

At the age of 3 years, his head circumference was 55 cm. Computerized tomography of the skull and brain showed that the anterior horn diameters were 60 mm and that the posterior horns were slightly unequal, the left lateral ventricle being larger than the right but there was no shift. At the age of 4 years, he required shunt revision. The blocked drain was not infected, and the ventricular CSF was normal. The proteinuria and other features of the nephrotic syndrome have not changed since diagnosis, but he is now in a condition of mild chronic renal failure. There was no history in any of the pregnancies of overt maternal illness, infection, excessive drug intake, or threatened abortion.

Autopsy of Fetus.—The fetus was of normal size for gestational age, and pathological findings were confined to the brain and kidneys. Gross hydrocephalus was present, affecting both lateral ventricles and to a lesser extent the third ventricle, with the cerebral cortex reduced to a mere 0.4-cm width. In the lateral ventricles, small white nodules were visible on the ependymal surfaces. Microscopy showed that much of the ependymal lining of the ventricles had been replaced by a cellular reaction that was raised focally to form a granular ependymitis (Fig 1). The aqueduct of Sylvius was obliterated close to the third ventricle without marked gliosis, but the lumen of the aqueduct was replaced by glial cells and nests of ependymal cells forming rosettes and aqueductules separated by edematous brain tissue (Fig 2).

Both kidneys measured 1.4 cm in length, and on microscopy, they contained many cysts distributed through both cortex and medulla but mainly deep cortical area. Some cysts were glomerular while others resembled primitive ducts and ductules (Fig 3). An active and apparently healthy zone of glomerulogenesis was present. Formed glomeruli were also present and appeared normal on light microscopy. Electron microscopy was not possible as preservation of the tissues was too poor for accurate assessment.

Renal Biopsy: Microscopic Findings.—Sections from the renal biopsy specimen showed excessive numbers of immature glomeruli, which were small and had tufts consisting of a prominent outer layer of epithelial cells with a few mesangial cells in the center. Other glomeruli appeared nor-

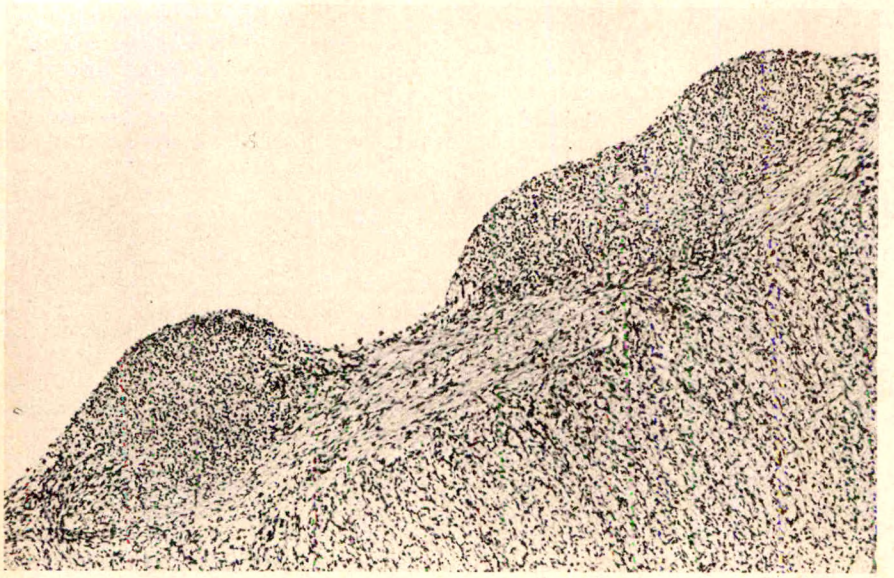

Fig 1.—Raised cellular nodules can be seen on ependymal surface of lateral ventricles (fetal autopsy findings). Level of destroyed ependyma is at base of nodules (hematoxylin-eosin, original magnification ×150).

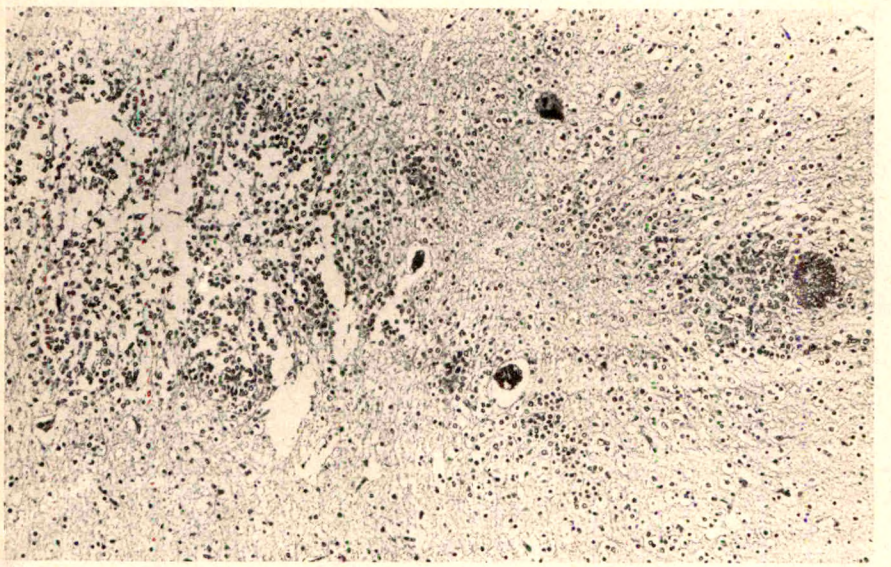

Fig 2.—Obliterated aqueduct of Sylvius showing replacement of glial cells and ependymal cells (fetal autopsy findings). Latter are forming rosettes. There is no observable increase in glial fibres (hematoxylin-eosin, original magnification ×150).

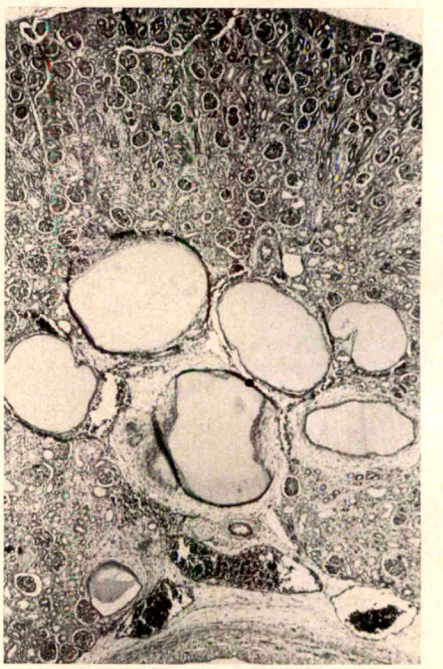

Fig 3.—Collection of cysts may be seen near corticomedullary junction of kidney. Renal pelvis is at bottom (hematoxylin-eosin, original magnification ×60).

mally developed, but there was a mild increase in mesangial cells and matrix with prominent capsular adhesions. Neither cysts nor dilated tubules were seen, and the glomerular basement membrane was normal. Electron microscopy showed foot process fusion and scattered, electron-dense deposits in the mesangium. Immunofluorescence studies demonstrated the presence of moderate quantities of mesangial and capillary loop C3 and IgM. The features were those of a mild, proliferative glomerulonephritis in a kidney containing many immature glomeruli.

Comment.—Interest in this set of siblings centers round the high amniotic fluid AFP levels for which no immediate cause was apparent. In neural tube defects, AFP reaches the amniotic fluid in excess either from a direct CSF leak or by passage across a defective membrane.[1] In instances where a small, skin-covered spinal lesion is present, the amniotic fluid AFP level is usually within normal limits.[2] A report[3] describing elevated amniotic AFP levels in association with isolated hydrocephalus has not been confirmed by others.[4] Known causes of elevated AFP level in the amniotic fluid, such as esophageal atresia, duodenal atresia, epidermolysis bullosa simplex, and exomphalos were excluded in our cases, leaving the possibility of congenital kidney disease with fetal proteinuria.

As the siblings had no gross external physical defect that would permit identification with one of the known syndromes in which hydrocephalus and renal lesions coexist, precise classification is not possible. The fact that the renal cysts in the fetus were not of the Potter type 3 category excludes diagnoses such as the syndrome of polycystic kidneys, internal hydrocephalus, and polydactyly.[5] Zellweger and the familial nephrotic syndromes should be carefully considered in the differential diagnosis. The cerebrohepatorenal syndrome of Zellweger comprises severe CNS defects (heterotopic cortex, periventricular cysts, and dysplastic changes in the olive and other areas), renal cortical (subcapsular) microcysts, and micronodular hepatic cirrhosis. Hydrocephalus has not been commonly found in this syndrome though one report mentioned mild dilation of the entire system[6] and

another[7] suggested that three infants with severe hydrocephalus and glomerular cysts may have suffered from the condition but the available data was too incomplete to allow confident diagnosis.

Affected infants have a characteristic facies with bossing of the forehead, and they have so far died by the age of 6 months.[8] In addition, the presence of hypotonia, failure to thrive, and cerebral dysfunction together with punctate calcification of cartilage are helpful in making the diagnosis during life. In the fetus from the third pregnancy, the liver was normal and the renal cysts closely resembled those found in previous cases of congenital nephrosis (Finnish type) seen at this institution.[9]

The results of the examination of the renal biopsy specimen of the surviving male infant, though not incompatible with the Finnish type of congenital nephrotic syndrome, showed no cysts, and the main features were those of a mild proliferative glomerulonephritis in a kidney still containing immature glomeruli at the age of 1½ years. He had a well-established nephrotic syndrome at the age of 16 months, and in view of the high amniotic fluid AFP level and the large placenta, it is likely that his kidney disease had an intrauterine onset. He shows no signs of liver pathology, and his present clinical course does not fit that described in the Zellweger syndrome or in congenital nephrosis (Finnish type).

Congenital nephrosis (Finnish type) is associated with high amniotic fluid and maternal serum AFP levels resulting from the glomerular leak of fetal serum protein,[9,10] which is thought to be due to faulty structure of the glomerular basement membrane. The condition is often, but not always, associated with microcysts of the tubules, particularly in the juxtamedullary area.[11] Congenital nephrosis (Finnish type) is usually fatal, and patients commonly die of infection in the first year or two of life though occasional infants survive longer. It always appears within 6 months of birth as the patients become symptomatic.

The course of this infant's unremitting nephrotic syndrome and the histopathological features are similar to those of the infantile-onset nephrotic syndrome that may be both familial and congenital.[12] It is suggested that this family has offspring who have both hydrocephalus and congenital renal disease associated with fetal and continuing postnatal massive proteinuria, ultimately becoming symptomatic as the nephrotic syndrome.

The familial nephrotic syndrome has been associated with congenital heart disease, deafness, urinary tract anomalies, and pyloric stenosis but is not associated with defects such as the gross hydrocephalus found in our three cases.[12] Although a spectrum of pathological changes occur in nonfamilial congenital hydrocephalus, aqueductal stenosis without substantial gliosis as seen in the fetus from the third pregnancy has been described in sex-linked congenital hydrocephalus,[13] and similar changes have been reported in experimental viral congenital hydrocephalus.[14,15]

In the female fetus, the fourth ventricle was not dilated but showed ependymal denudation similar to the grossly enlarged lateral and third ventricles so that a suspicion of inflammatory etiology is present. We have no histological information regarding the state of the male infant's ventricular systems to compare with the details available in the fetus. If intrauterine infection is the etiological factor in the fetal hydrocephalus, it must also be suspected of contributing to the hydrocephalus in the other two siblings. The maternal infection would therefore have to be present during a four-year period, with apparently no overt flare-up during pregnancy and no recognizable immunological reaction. However, there was definitely no history of maternal illness during the last pregnancy. In addition, most intrauterine infections leading to CNS abnormalities are also responsible for severe mental retardation with foci of cerebral necrosis and calcification. The male infant has no sign of these.

An autosomal recessive trait could explain all our cases and be responsible for a hitherto unrecognized syndrome of isolated hydrocephalus with associated familial nephrotic syndrome. The latter has a milder course than the Finnish type of congenital nephrosis and, like it, can be diagnosed antenatally. Elective termination of pregnancy may be indicated.

Confirmation of new syndromes can only be established when many cases are reported with similar features. We do not believe that any of our cases fits into predescribed categories and suggest that this may be a new syndrome. We cannot give precise etiology (genetic or environmental) but believe that others may have seen similar cases that would permit classification. As antenatal diagnosis is possible, there is further reason for the prompt elaboration of the syndrome.

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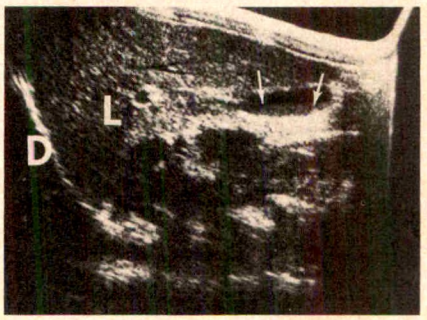
1. Brock DJH: Prenatal diagnosis: Chemical methods. *Br Med Bull* 32:16-20, 1976.
2. Ferguson-Smith MA, Vince JD: Observations on prenatal screening for spina bifida in Glasgow. *Br J Obstet Gynecol* 83:329-332, 1976.
3. Seppälä M, Unnerus HA: Elevated amniotic fluid alpha fetoprotein in fetal hydrocephaly. *Am J Obstet Gynecol* 119:270-272, 1974.
4. Williamson EM, Siggers DC, Miller JF: Amniotic fluid alpha fetoprotein and congenital hydrocephalus. *Br Med J* 2:1450, 1976.
5. Simoupoulos AP, Brennan GG, Alwan A, et al: Polycystic kidneys, internal hydrocephalus and polydactylism in newborn siblings. *Pediatrics* 39:931-934, 1967.
6. Sommer A, Bradel EJ, Hamoudi AB: The cerebro-hepato-renal syndrome (Zellweger's syndrome). *Biol Neonate* 25:219-225, 1974.
7. Danks DM, Tipott P, Adams C, et al: Cerebro-hepato-renal syndrome of Zellweger. *J Pediatr* 86:382-387, 1975.
8. Gilchrist KW, Gilbert EF, Shahidi NT, et al: The evaluation of infants with the Zellweger (cerebro-hepato-renal) syndrome. *Clin Genet* 7:413-416, 1975.
9. Wiggelinkhuizen J, Nelson MM, Berger GMB, et al: Alpha-fetoprotein in the antenatal diagnosis of the congenital nephrotic syndrome. *J Pediatr* 89:452-455, 1976.
10. Kjessler B, Johansson SGO, Sherman MS, et al: Alpha-fetoprotein in antenatal diagnosis of congenital nephrosis. *Lancet* 1:432-433, 1975.
11. Hallman N, Norio R, Rapola J: Congenital nephrotic syndrome. *Nephron* 11:101-110, 1973.
12. Moncrieff MW, White RHR, Glasgow EF, et al: The familial nephrotic syndrome: A clinicopathological study. *Clin Nephrol* 1:220-229, 1973.
13. Bickers DS, Adams RD: Hereditary stenosis of the aqueduct of Sylvius as a cause of congenital hydrocephalus. *Brain* 72:246-262, 1949.
14. Johnson RT, Johnson KP: Hydrocephalus following viral infection: The pathology of aqueductal stenosis developing after experimental mumps virus infection. *J Neuropathol Exp Neurol* 27:591-606, 1968.
15. Margolis G, Kilham L: Experimental virus-induced hydrocephalus. *J Neurosurg* 31:1-9, 1969.

Cholelithiasis Associated With the Hemolytic-Uremic Syndrome

The hemolytic-uremic syndrome (HUS) exhibits a prodrome characterized by prominent gastrointestinal (GI) symptoms including vomiting, diarrhea that is often bloody, and colicky abdominal pain.[1-3] Persistent vomiting and abdominal pain continued after return of normal renal function and cessation of hemolysis in a 15-year-old girl with severe HUS. She was found to have cholecystitis because of calcium bilirubinate stones, which developed as a consequence of hemolysis. Cholelithiasis occurring as a complication of HUS has not previously been reported.

Report of a Case.—A previously healthy 15-year-old girl had anuria after five days of vomiting and bloody diarrhea. The diagnosis of HUS was made because of renal failure, anemia, thrombocytopenia, and the presence of many schistocytes on peripheral smear. The patient was then transferred to the Children's Hospital of Michigan, Detroit, where she remained anuric for 11 days. She required eight hemodialysis treatments and four transfusions of packed RBCs. Platelet counts first increased to more than 100,000/cu mm nine days after admission. Hemolysis slowly decreased, and by three weeks after admission, the serum haptoglobin level and peripheral blood smear were normal. Renal function improved, and her serum creatinine level stabilized at 0.7 mg/dL five weeks after admission. Results of hemoglobin electrophoresis and glucose-6-phosphate dehydrogenase assay, hemoglobin level, reticulocyte count, and peripheral smear findings were all normal several months after admission.

Despite improvement in hematologic and renal manifestations, severe anorexia and nausea continued. Nonbilious vomiting occurred whenever oral feeding was attempted. Physical examination showed moderate epigastric and right subcostal tenderness. Results of upper GI examination and liver function tests were normal. Serum amylase level was 350 to 400 units/dL (normal, 50 to 200 units/dL) (Amylotube method), and serum lipase value was 8.8 Cherry-Crandall units/dL (normal, 0 to 1.5 units/dL). Ultrasound examination demonstrated a normal pancreas, but it showed multiple opacities within a nondilated gallbladder (Figure). Normal-sized ducts were visualized on intravenous cholangiography. A two-week trial of conservative medical therapy was unsuccessful, and, consequently, a cholecystectomy was performed. No abnormalities of the pancreas were observed, and no adhesions and minimal inflammatory reaction were noted. Multiple small calcium bilirubinate stones and sludge were found in the gallbladder that was chronically inflamed and



Supine longitudinal ultrasonic scan of liver and gallbladder shows normal liver (L) and gallbladder that has multiple densities at its base (arrows). There was no shadowing behind gallbladder. On sonographic examinations in erect position, opacities did not move to most inferior surface of gallbladder. Nonshadowing nature of opacities and failure to move rapidly with gravity supports diagnosis of abnormal ultrasound with sludge (category 3).[11] D indicates diaphragm.

that had slightly thickened walls with minimal fibrosis. Intraoperative cholangiography with visualization of the pancreatic ducts showed no abnormalities. The surgical and pathologic findings are consistent with gallbladder disease of less than two months' duration. Recovery was uneventful. Despite absence of abdominal symptoms, the serum amylase level remained elevated (> 300 units/dL) until eight weeks postoperatively. During this period, an amylase clearance to creatinine clearance ratio was 1.27% (normal, 1% to 4%).[4,5] The serum creatinine clearance remained 0.7 mg/dL.

Comment.—Persistence of GI symptoms in a patient with HUS is unexpected after improvement of the renal and hematologic manifestations.[1-3] The elevated levels of serum amylase and lipase in this patient led to a tentative diagnosis of pancreatitis, and an abdominal ultrasound scan was obtained. The findings of nonshadowing opacities within the gallbladder and a normal-appearing pancreas explained the cause of the abdominal symptoms. The elevated serum amylase level can be attributed to decreased renal amylase clearance associated with the renal insufficiency of the HUS,[5,6] to the demonstrated biliary tract disease,[4] or to a combination of the two.

Since cholelithiasis is uncommon in this age group[7] and there was no history of unusual abdominal complaints nor evidence of a chronic hemolytic process, the gallstones seemed to have recently formed. The presence of gallstones in patients with chronic hemolytic processes, such as sickle cell disease and hereditary spherocytosis, is well known.[8,9] Neither is cholelithiasis mentioned as a complication of the HUS,[1-3] nor is an acute hemolytic process listed in several recent reviews of the etiology of gallstones.[7,10] The demonstration of gallbladder contents consisting of microcrystalline calcium bilirubinate calculus fragments supports the hypothesis that the acute hemolytic episode was the pathophysiologic event leading to cholelithiasis. Pigment gallstones should be suspected as a cause of abdominal pain in patients with acute, as well as chronic, hemolytic diseases, and they can be easily and safely looked for using ultrasonic scanning techniques.

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1. Whitington PF, Friedman AL, Chesney RW: Gastrointestinal disease in the hemolytic-uremic syndrome. *Gastroenterology* 76:728-733, 1979.

2. Lieberman E: Hemolytic-uremic syndrome. *J Pediatr* 80:1-16, 1972.

3. Gianantonio CA: Hemolytic-uremic syndrome, in Edelmann CM Jr (ed): *Pediatric Kidney Disease*. Boston, Little Brown & Co, 1978, pp 724-736.

4. Salt WB, Schenker S: Amylase: Its clinical significance. *Medicine* 55:269-289, 1976.

5. Tedesco FJ, Harter HR, Alpers DH: Serum amylase determinations and amylase to creatinine clearance ratios in patients with chronic renal insufficiency. *Gastroenterology* 71:594-598, 1976.

6. Berk JE, Fridhandler L, Ness RL: Amylase and isoamylase activities in renal insufficiency. *Ann Intern Med* 90:351-353, 1979.

7. Sleisenger MH, Fordtran JS: *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. Philadelphia, WB Saunders Co, 1978, pp 1248-1263.

8. Sarnaik S, Slovis T, Corbett D, et al: Incidence of cholelithiasis in sickle-cell anemia using the grey-scale ultrasonic technique. *J Pediatr*, to be published.

9. Bates GC, Brown CH: Incidence of gallbladder disease in chronic hemolytic anemia (spherocytosis). *Gastroenterology* 21:104-109, 1952.

10. Bennion LJ, Grundy SM: Risk factors for the development of cholelithiasis in man. *N Engl J Med* 299:1161-1166, 1221-1226, 1978.

11. Crade M: Comparison of ultrasound and oral cholecystogram in the diagnosis of gallstones, in Taylor KJW (ed): *Diagnostic Ultrasound in Gastrointestinal Disease*. New York, Churchill Livingstone, 1979, pp 123-135.

Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

Infantile Cholestatic Liver Disease

Sir.—We read with interest the report by Rosenthal et al (JOURNAL 133:1195-1196, 1979) concerning infantile cholestatic liver disease associated with alpha$_1$-antitrypsin deficiency and the Pi-SZ phenotype. We have seen a similar patient who at 1 month of age had failure to thrive and conjugated hyperbilirubinemia. The only other clinical abnormality was a cholesterol level of 415 mg/dL. Rose bengal sodium I 131 did not enter the intestine.

An operative cholangiogram and open biopsy were performed before the results of the alpha$_1$-antitrypsin estimation were known. Bile ducts were present, but some observers thought they were small. Histologically, there was some increase in hepatic ducts and mononuclear infiltration. Diastase-resistant, PAS-positive granules were seen in both hepatocytes and Kupffer's cells. The alpha$_1$-antitrypsin level was estimated to be 90 mg/dL by radial immunodiffusion. The infant's Pi type was SZ, the father's SS, and the mother's MZ. By 2 months of age, the total bilirubin level was 3.3 mg, with the direct at 0.1 mg/dL, and the cholesterol was 292. At 5 months of age he was growing well and the cholesterol level had fallen to 164 mg/dL.

We had been concerned with the specificity of the histological examination of the liver biopsy specimen using PAS and diastase. Sections from a number of patients with jaundice, including galactosemia, unexplained fibrosis, hepatic ductular hypoplasia, and neonatal hyperbilirubinemia were prepared and stained in the same way. All of these patients had normal or elevated levels of alpha$_1$-antitrypsin. We could not detect any difference in the appearance of the PAS-positive granules between any of these samples and that from the infant with the SZ phenotype. We noticed that in published, later biopsy material, the granules are larger and there are clear halos around them. We wonder if other investigators have been similarly confused, particularly in light of the recent report of similar granules in a family with the Dubin-Johnson syndrome.[1]

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1. Lo NS, Chan CW, Hutchison JH: Dubin-Johnson syndrome with some unusual features in a Chinese family. *Arch Dis Child* 54:529-533, 1979.

The Danger of 50-mg Dapsone Doses to Children

Sir.—In reference to the article "Bullous Disease of Childhood" by Ramsdell et al (JOURNAL 133:791-794, 1979), please correct an error. Fifty milligrams of dapsone twice daily is *not* the correct dosage for the treatment of bullous disease of childhood (or any other disease of childhood). Childhood weight varies from about 2 to 80 kg. Because the common side effects of dapsone, namely, methemoglobinemia and hemolysis, are usually dose-related, the dosage of this drug should be calculated on a body-weight basis. The authors' use of 250 mg of dapsone per day in the treatment of their first patient, an 18- to 20-month-old child, seems excessive to me; later the dosage was lowered.

The dosage recommended to one of the authors by me as early as 1976[1] is 2 mg/kg. The dangers of a larger dosage were pointed out to me in conversation with R. Caputo, MD (Jan 11, 1979). He began treatment with a 4 mg/kg dose; within 24 hours, severe methemoglobinemia and hemolysis developed. The greater danger of casually presenting the 50-mg dapsone dose to the medical profession via this article became evident on Aug 24, 1979, just a few days after its publication, when Dr Virginia Weiss told more than 300 physicians at the International Congress of Pediatric Dermatology, Chicago, that the proper dosage for dapsone is 50 mg. Her source of information? The latest issue of the JOURNAL! I would appreciate knowing why the authors chose this dose.

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1. Kahn G, Rywlin AM: Acropustulosis in Infancy. *Arch Dermatol* 115:831-833, 1979.

In Reply.—We accept Dr Kahn's recommendation of 2 mg/kg/day as a reasonable and safe starting dosage of dapsone for the various dapsone-responsive dermatoses, including bullous disease of childhood and dermatitis herpetiformis. We agree that a milligram-per-kilogram dosage schedule for diseases that may occur at various ages (and body weights) is a more acceptable method of prescribing.

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This new guide outlines the major functions of an emergency medical services plan, plus the key elements in providing such services, which should be common to all airports. Includes illustrations and appendices.

Books

Neonatal Surgery, ed 2, edited by P. P. Rickham, James Lister, and Irene M. Irving, 621 pp, $99.95, Boston, Butterworth Inc, 1978.

The 23 authors from Liverpool and Zurich have compiled a very interesting 50 chapters, organized to cover most of the conditions encountered by the pediatric surgeon who cares for the neonate. Each chapter has been well referenced by its author, and the numerous photographs from his or her personal experience add much to the clarity of the text. The first of eight parts is entitled "General" and covers a wide range of topics, from Dr Rickham's views on ethics to Nurse Hartley's suggestions on nursing care of the neonate. Part 2 covers trauma, tumors, and twins, each being covered concisely and expertly. The more unusual are covered in a brief but adequate way. Part 3, entitled "Head and Neck," succinctly covers the surgical approach to a few conditions that might require emergency surgery. Part 4 covers the rib cage, diaphragm, and lungs. The chapters on diaphragmatic hernia and esophageal atresia are especially well done. Part 5 covers the heart and great vessels. A large amount of information is presented, describing the lesion, its surgical therapy, and the postoperative care. In Part 6, the abdominal wall, alimentary, and biliary systems are presented, with the common and the unusual conditions being described. Here, especially, the influence of P. P. Rickham is apparent in the surgical technique. Part 7 encompasses the early management of congenital CNS lesions, such as myelomeningocele. Part 8 briefly covers the urogenital system, including intersexuality.

The book's editors have managed to use the book's 621 pages to their best advantage. Admittedly, some subjects are covered very briefly, but the reference list provides an adequate reading list for the reader in need of more information.

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Neonatal Respiration, by L. B. Strang, 316 pp, $36.50, Philadelphia, JB Lippincott Co, 1977.

The science of neonatal respiration was spawned and nurtured to its current vigorous growth within the professional life spans of many current investigators, none of whom has contributed more to the study of developmental respiratory physiology than the author of this cogent book, L. B. Strang. The valuable longitudinal perspective afforded by a veteran and keen observer of a specialty science is often lost in the multiauthored or edited textbooks circulating today. That Dr Strang has decided to write a treatise on such a large and dynamic field as neonatal respiration is thus warmly welcomed by fellow students of the physiology of the newborn.

This is an excellent book. First of all, it is reassuring to note that it is possible, at some cost no doubt, to remain sufficiently abreast of all major subsets of one's specialty to write concise, orderly, lucid, well-illustrated, and well-referenced topical chapters that are suitable for both clinicians and researchers in the field. Second, the fact that the chapters are contained in a compact and relatively inexpensive book is a further recommendation.

The discussions of surfactant, pulmonary circulation at birth and of neonatal lung edema were my particular favorites; they have served well as outlines for clinical teaching. Apnea received less attention than is warranted by its clinical significance, and I am rather less impressed with the contribution of milk aspiration to clinical morbidity than is the author. The appended chapter on intravenous feeding seems out of place.

Principles of respiratory physiology intrude increasingly into the bedside formulation of clinical patient management in neonatal intensive care units. This book should prove to be a valuable clinical tool.

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Synopsis of Pediatrics, edited by James G. Hughes, 915 pp, $21.50, St Louis, CV Mosby Co, 1980.

Bigger and better, this fifth edition of a popular pediatrics book outgrows its designation of being a "synopsis" and emerges as a major, even though abbreviated, textbook that covers the essentials of the medical care of infants and children.

In a preface to the first edition, Dr Hughes indicated that his intention was to solve the riddle of combining brevity and clarity with a proper degree of comprehensiveness. In this edition, he has succeeded. The 32 chapters cover the field of pediatrics in a traditional fashion and in this edition two new chapters appear: "Adolescence" and "Child Abuse and Neglect." From the first edition through this one, the temptation to treat problems in a "cookbook" fashion has been resisted: mechanisms and reasons for disease, with a clear delineation of principles of treatment, have been used throughout. Nowhere is this better illustrated than in the outstanding chapter, "Common Fluid and Electrolyte Problems in Pediatrics," by James N. Ettledorf, MD, the master teacher who also took responsibility for this chapter in all other editions. In this chapter one will find, in only 13 pages, the principles that will allow the student or physician to manage and understand fluid and electrolyte problems in pediatrics. How the editor managed to get his 37 contributors to combine a practical thoroughness with brevity when writing their assignments is a secret that other editors should explore. All of the contributors have been or are associated with the University of Tennessee Center for

the Health Sciences, except Harry S. Shirkey, MD, who contributed the chapter on drugs in table form.

Careful editing, probably combined with much rewriting, has resulted in a clear style with unusual uniformity. Although the book contains 100 fewer pages than the previous edition, it is slightly larger in horizontal and vertical dimensions and has a new double column format that makes for easier reading. More tables, graphs, and photographs are used than previously. The book is bound in stain- and water-resistant material. It is unusually handsome, outside and in, and the publishers can present it with pride.

It is difficult to define the overall place of an abbreviated textbook of pediatrics. The author never intended that the book should replace the more conventional ones that have become distressingly more expensive as they grow larger and larger. This book will fill the needs of many physicians who want up-to-date knowledge on most pediatrics subjects. It is a handy and useful book to have around a hospital floor, a clinic, or in a physician's office. For those who feel that they cannot afford every new edition of traditional textbooks, it is also an economical way to have current knowledge at hand.

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The Divorced Family (three-volume series), by Francine Spilke, 80, 82, and 32 pp, $6.95 each, New York, Crown Publishers Inc, 1979.

Current statistics are sobering: approximately 40% of marriages end in divorce. Five years after a divorce, 37% of children display severe psychiatric symptoms. The commonplace nature of divorce, its acceptance in everyday life, and its frequent treatment by television programs and popular movies have not diminished the need of parents and children for specific advice in coping with the stress associated with family disruption.

Francine Spilke, a discussion leader for groups of divorced parents and children, has written a set of three short books, the stated purpose of which is to "try to prevent children from becoming victims of their parents' divorce." The set is composed of a storybook for preschoolers, a book intended for older children and adolescents, and a parents' manual.

The storybook is entitled *The Family That Changed*, and violates Ms Spilke's own recommendation to avoid overloading the child with too much information at one sitting. There are acceptable ways to explain an impending divorce to one's young child, but to sit down with him and read aloud "Your mommy and daddy are not going to be married to each other anymore" seems unnatural and misguided. Other currently available storybooks (my favorite is Joan Lexau's *Emily and the Klunky Baby and the Next-Door Dog*, Dial Press, 1972) provide a better basis for explaining the implications of divorce.

What About Me? is written for children aged 9 to 15 years and more successfully deals with the feelings that separation engenders in both children and parents. It also deals sensitively with the issues of visits with the noncustodial parent and remarriage. Children are wisely advised to discuss with their parents the information offered in each chapter. The book suffers, however, from being written for different levels of development, and thus at times may appear either overly juvenile or too sophisticated. Many different family arrangements and problems are discussed that may not be pertinent to an individual child's situation.

What About the Children? is intended as a parents' handbook, but offers the same format and often the same information as the previous book. The author's intention is to provide insights into how children may behave under the stress of separation, and how some parents may conduct themselves to cause further problems for their children. Although parents are often very troubled at the time of divorce, this book assumes that the divorce occurs under ideal circumstances: amicable parents who respect themselves and each other, well-loved children, and solid parent-child relationships. Some valuable practical suggestions are given regarding the moving out of a parent, visiting days, and shared experiences between children and noncustodial parents. The effects of divorce on very young children are not dealt with, but the author successfully demonstrates the potentially harmful effects of disrupted parenting on older children.

These books are of uneven value. I do not recommend *The Family That Changed. What About the Children?* may be of limited value to professionals in terms of its practical insights. As a self-help guide, it will be read with interest by some insightful parents. *What About Me?*, however, is a more useful book and, while written for older children, it could probably be used to better advantage by parents as a guide to understanding children's feelings.

HAROLD A. KANTHOR, MD
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Book in Brief

Intoxications of the Nervous System, part 2, vol 37, *Handbook of Clinical Neurology*, edited by P. J. Vinken and G. W. Bruyn (578 pp, Amsterdam, North-Holland Publishing Co, 1979) (price not stated). A companion to volume 36 (see previous review), this multiauthored volume deals with a variety of intoxicants. Of particular interest to pediatricians are the chapters devoted to salicylisms and to hexachlorophene toxicity; one is reminded of the fact that this latter material is absorbed through the skin in amounts sufficient to cause CNS damage.

There is an interesting chapter on Jamaican vomiting sickness (which, incidentally, has some features in common with Reye's syndrome, such as hypoglycemia, fatty liver, and CNS edema) that is now known to be caused by the ingestion of uncooked unripe ackee, a fruit found in Central America, West Africa, and southern Florida as well as Jamaica. The intoxicant turns out to be an α-amino acid of unusual structure, called hypoglycin A, which interferes with gluconeogenesis, leucine metabolism, and acyl-CoA dehydrogenases. Additional chapters discuss other intoxicants: snake venoms, marine toxins, poisonous insects, antiepileptic and psychotherapeutic drugs, CNS stimulants, and organophosphates.

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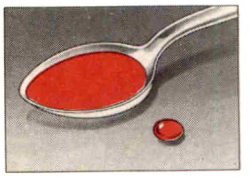

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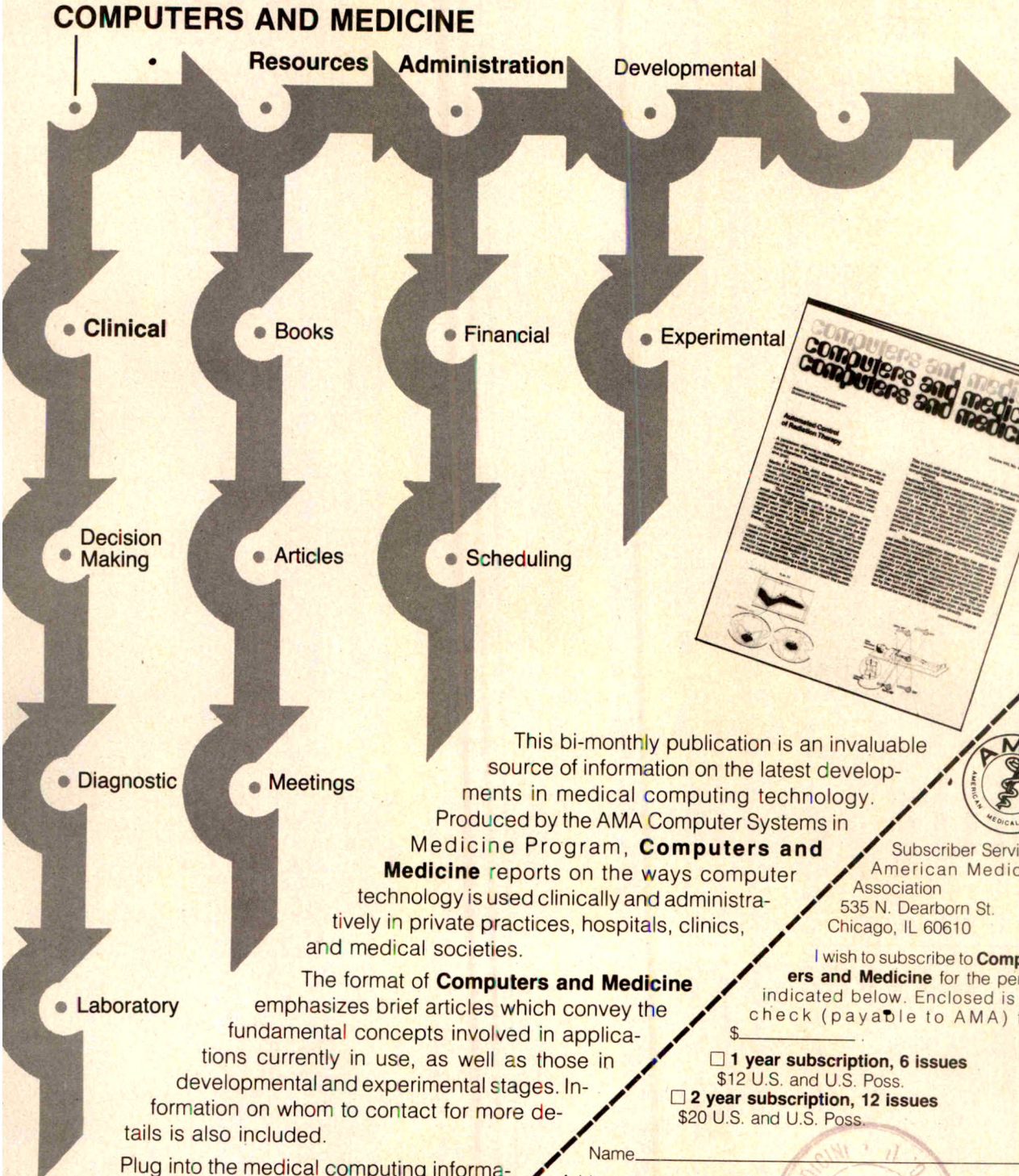

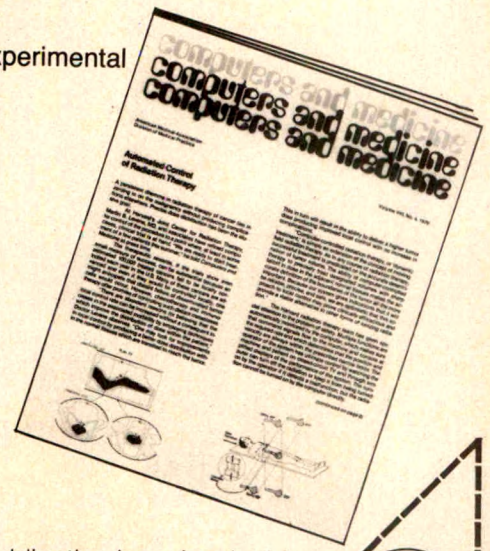

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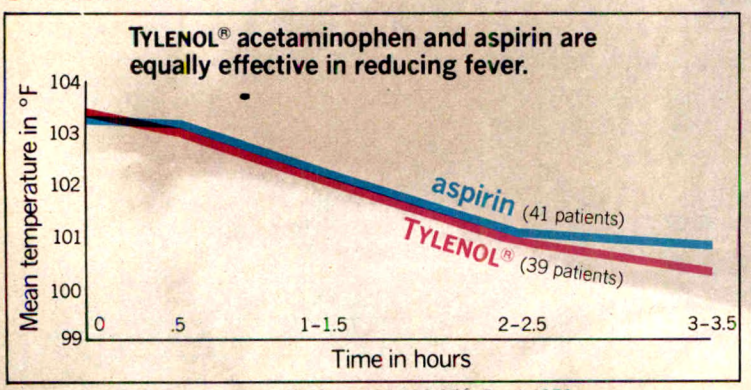

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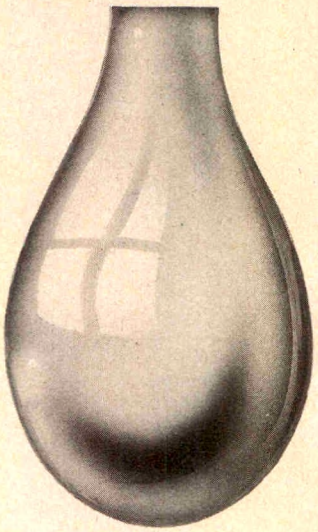

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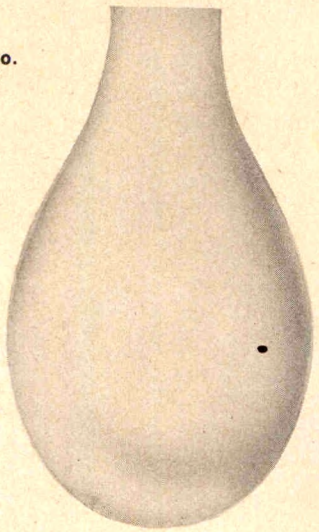

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Congenital Toxoplasmosis

Toxoplasmosis, an infection caused by the protozoan parasite *Toxoplasma gondii* occurs in many species of mammals and birds throughout the world. In man, toxoplasmosis is a very common infection with a prevalence ranging anywhere from 5% to 95% among young adults living in different parts of the world.[1] In the United States, by the end of the fifth decade of life, approximately 50% of the population is asymptomatically, yet chronically infected. Despite this high prevalence, the diagnosis of toxoplasmosis is only rarely entertained as the cause of illness. However, the clinical importance of this infection derives from the fact that it may mimic a variety of clinical syndromes, it may cause severe, even fatal infection in the immunologically compromised host, or as we are reminded by Dr Stray-Pedersen in this issue of the JOURNAL (p 638) that, *T gondii* may be transmitted from mother to fetus.[1-4]

OCCURRENCE OF CONGENITAL TOXOPLASMOSIS

Because congenital toxoplasmosis occurs only when maternal infection is first acquired during pregnancy, defining the risk of acquisition is of paramount importance if one is to assess the magnitude of this problem.[3] After prospectively studying more than 8,000 pregnant women, the Oslo study demonstrated that the rate of acquisition of toxoplasmosis during pregnancy was 1.1 to 1.3 per 1,000 pregnant women. By contrast, in the United States the rate of seroconversion in the general population between the ages of 15 and 35 years, is 1.25% to 1.2% per year.[1] Thus, we can anticipate that approximately six of every 1,000 pregnant women will acquire toxoplasmosis during the nine months of gestation. A recent study from the Oregon Public Health Laboratory has confirmed these figures after testing nearly 100,000 pregnant women over a six-year period. In this study, seroconversions occurred at a rate of 0.63% per year or in one of every 200 pregnancies.[5] Despite these high figures, the rate of congenital toxoplasmosis in the United States ranges between two and one per 1,000 live births. Two prospective studies performed in this country, one in Birmingham, Ala and the other in New York City showed an incidence of one per 750 and one per 1,350 live births, respectively. If these figures are extrapolated to the population at large, then an estimated 3,300 infants are born each year with congenital toxoplasmosis.[1]

In this issue of the JOURNAL, Dr Stray-Pedersen reports that three of 11 mothers who acquired toxoplasmosis during pregnancy transmitted the infection to their unborn babies. Previous studies, namely those of Remington and Desmonts[1] and Desmonts and Couvreur,[3] had established that nearly 45% of women who acquire toxoplasmosis during pregnancy give birth to congenitally infected infants. The rate of transmission is directly related to the gestational age at the time of infection. For instance, in the French study the incidence of fetal infection went from 17% to 25% to 65% when maternal toxoplasmosis was acquired during the first, second, and third trimester of gestation. However, as one might expect, fetal damage was inversely related to gestational age. This phenomenon explains why the majority of infants born with congenital toxoplasmosis appear normal or only moderately sick at birth. Previous studies have established that 70% of the infants born with this infection are asymptomatic, 10% are born with ocular involvement only, and the remaining 20% suffer from a symptomatic infection that manifests itself as either an acute generalized form of illness or as neurologic sequelae.[1,4] In Dr Stray-Pedersen's study, only one of the three infants with congenital toxoplasmosis was recognized as having hepatomegaly at birth.

Despite early diagnosis and treatment, the more severe form of congenital toxoplasmosis leads inevitably to debilitating sequelae like impaired vision and psychomotor retardation. However, of greater medical importance is the fact that the subclinical form of this disease may also lead to serious untoward sequelae.[2,4] In our personal experience, chorioretinitis, which in some cases results in blindness, or varying degrees of mental retardation have developed in most patients who were asymptomatic at birth. These findings, gathered after years of tedious longitudinal studies, indicate that despite its low incidence congenital toxoplasmosis is a significant health hazard.

NEED FOR ACCURATE DIAGNOSIS

The first step in preventing the deleterious effects of congenital toxoplasmosis is accurate diagnosis. The study published in this issue together with a fairly impressive body of information published by several investigators in both Europe and the United States, demonstrate the need for a widely applicable serologic method to test for acute toxoplasmosis during pregnancy. Since congenital toxoplasmosis occurs only when the infection is first acquired during gestation, the documentation of antibodies before conception indicates there is no risk of fetal infection in a future pregnancy. Conversely, a seronegative woman must be considered susceptible; in the United States nearly 80% of pregnant women will fall into this category (this is the rate of susceptibility at approximately 20 to 25 years of age).[1] Since in the vast majority of cases acute *Toxoplasma* infections are asymptomatic, serial determinations of antibody would be required to identify primary infections during gestation. These measurements can be done by several different assays, but clearly the most widely accepted are indirect immunofluorescence and Sabin-Feld-

man dye tests. A serious dilemma is posed by those pregnant women who have a high antibody titer on their first prenatal visit; (titers of ≥ 1,024 suggest recent infections). The most important diagnostic aid in these cases is the determination of specific IgM antibodies.[1] Dr Stray-Pedersen provides additional support to this approach since ten of the 11 women considered at high risk by the more classic serologic assays were also positive in the fluorescent antibody (FA)-IgM tests. In contrast, none of the 23 patients considered at minimal risk possessed IgM antibodies. In the past, as in Dr Stray-Pedersen's study, attempts at prenatal diagnosis of fetal infection by means of determinations of IgM antibodies in amniotic fluid have been unsuccessful. However, her report of isolation of *T gondii* from the amniotic fluid in two of the three confirmed cases of congenital toxoplasmosis must be viewed as a contribution of major significance. *Toxoplasma* organisms can be isolated by inoculation into mice or monolayers of tissue cultures. The latter method is of particular value because it is becoming more and more available due to the rapid expansion of diagnostic virology laboratories. Clearly, larger studies should be undertaken in the future to better define the value of this diagnostic approach.

It is obvious that the recognition of acute toxoplasmosis during pregnancy and more specifically the recognition that fetal infection has occurred could lead to therapeutic intervention. For this purpose European investigators have used spiramycin, an antibiotic that is not available in the United States. Their results have not been very successful due primarily to poor transplacental transfer. An alternative is the use of pyrimethamine (Daraprim) and sulfadiazine, a combination of proven efficacy. However, because it is potentially teratogenic the use of this drug combination must be carefully pondered, particularly in the first trimester of pregnancy. If treatment is to be given during this period, most investigators recommend the use of sulfonamide drugs alone. Finally, and only after an irrefutable diagnosis of toxoplasmosis acquired during the first trimester is made, one could consider therapeutic abortion.

The diagnosis of congenital toxoplasmosis after birth is normally made by demonstrating persisting or rising levels of specific IgG antibodies, by the presence of IgM antibodies in cord or neonatal sera, or by isolating *Toxoplasma* organisms from placenta or cord blood.[1,4] Of these methods, serial determination of IgG antibodies is the only one that is readily available to most clinicians. Its main drawback is the four to six months required to confirm the diagnosis, a delay that is undesirable in view of the progressive nature of this disease. The use of the FA-IgM test has had supporters and detractors, but for all practical purposes the results of this test in diagnostic laboratories are generally unreliable due to a variety of technical problems. This contention is further supported by Dr Stray-Pedersen's observations that none of the three infants with congenital toxoplasmosis had specific IgM antibodies on their cord sera nor did a measurable IgM response develop afterwards. In contrast, in two of these cases *Toxoplasma* organisms were isolated from placenta. Hopefully this particular method will be further investigated in the future.

Diagnostic evaluations are normally entertained only for those patients in whom the diagnosis of congenital toxoplasmosis is suspected on clinical grounds. This means that approximately 80% of all infants born with this infection would never be identified until perhaps years later when untoward sequelae become apparent. This is the rationale behind the programs for screening asymptomatic neonates. Those that have been proposed include the simple quantification of IgM in cord sera or the detection of *Toxoplasma* IgM antibodies in the same specimen.[4] Due to their low sensitivity and poor specificity neither has achieved broad acceptance.

Because of these diagnostic difficulties, in the past two years Dr Stray-Pedersen as well as two groups of investigators in the United States and France have tried to ascertain the diagnostic value of an assay that measures the blastogenic response of lymphocytes incubated with *Toxoplasma* antigens.[6,7] The rationale behind this approach is that lymphocyte transformation reflects a specific immune response in the newborn and does not appear to be influenced by maternal immunity. This technique could prove particularly valuable during the first six months of life, a period in which maternally derived IgG antibodies interfere with serologic diagnosis. The number of patients studied by these groups of investigators is simply too small to reach a definitive conclusion. The results, to date, are somewhat disappointing. Dr Stray-Pedersen tested two of the three congenitally infected infants during their first year of life and found that both were negative. At 12 months of age the lymphocytes from all three patients responded but only minimally. Wilson et al[7] reported that 21 of 25 patients with congenital toxoplasmosis had a positive lymphocyte transformation response. It is noteworthy, however, that two of the negative responses occurred among the three infants tested between 1 and 3 months of age. In our study that included 13 patients, all gave a positive result but none was less than 1 year of age at the time of evaluation. Thus, it seems that assessing cell-mediated immunity, at least with a lymphocyte transformation assay, during the first 4 months of age is not much better than the serial detection of IgG antibodies by indirect immunofluorescence or Sabin-Feldman dye tests.

These difficulties in establishing the diagnosis of congenital *Toxoplasma* infection in asymptomatic infants have seriously limited the performance of studies to determine the efficacy of treatment. Although the incidence of congenital toxoplasmosis is low and the damage limited, I am convinced that these issues will need to be addressed in the future. If massive screenings can be standardized and performed at a reasonable cost, the best strategy would be to screen for primary toxoplasmosis during pregnancy. This would give us the opportunity for therapeutic intervention immediately or soon after the fetus is infected. If this is not feasible

or turns out to be too expensive, then neonates may have to be tested by serologic or other means. None of the methods now available to the clinician are specific and sensitive enough to meet the criteria for a massive screening program of newborn infants.

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References

1. Remington JS, Desmonts G: Toxoplasmosis, in Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, WB Saunders Co, 1976, pp 191-332.

2. Stagno S, Reynolds DW, Amos CS, et al: Auditory and visual defects resulting from symptomatic and subclinical congenital cytomegalovirus and toxoplasma infections. *Pediatrics* 59:669-678, 1977.

3. Desmonts G, Couvreur J: Congenital toxoplasmosis: A prospective study of the offspring of 542 women who acquired toxoplasmosis during pregnancy—pathophysiology of congenital disease, in Thalhammer O, Baumgarten K, Pollack A (eds): *Perinatal Medicine, Sixth European Congress, Vienna 1978*. Stuttgart, West Germany, Georg Thieme Publishers, 1979, pp 76-89.

4. Alford CA Jr, Stagno S, Reynolds DW: Congenital toxoplasmosis: Clinical, laboratory, and therapeutic considerations, with special reference to subclinical disease. *Bull NY Acad Med* 50:160, 1974.

5. Beach PG: Prevalence of antibodies to *Toxoplasma gondii* in pregnant women in Oregon. *J Infect Dis* 140:780-783, 1979.

6. Pass R, Reynolds DW, August A, et al: Cellular immune response to toxoplasma in children with congenital toxoplasmosis (CT), abstracted. *Clin Res* 27:810A, 1979.

7. Wilson CB, Desmonts G, Couvreur J, et al: Lymphocyte transformation in diagnosis of congenital toxoplasma infection, in: *Program & Abstracts, 19th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 1-5, 1979*, abstract No. 449.

60 YEARS AGO IN THE AJDC

Active Immunization Against Diphtheria in a Large Child-Caring Institution

In the Home for Hebrew Infants in New York City diphtheria had been an endemic disease for a number of years. The year 1915 saw the death of six children from the disease, in addition to many more clinical cases that occurred. The Schick test, first used in 1908 and published in 1913, was used by Dr Blum to determine the susceptibility of children to diphtheria. (An inflammatory reaction at the site of injection of diphtheria toxin into the skin indicates tissue antibody is insufficient to neutralize the injected toxin.) Of 1,076 children tested, 37.7 per cent. had positive Schick tests. Among infants 1 to 6 months, 21.6 per cent. had positive Schick tests. In infants 6 months to 1 year, 62.6 per cent. had positive Schick tests. In those children 4 to 6 years of age, 20.9 per cent. had positive Schick tests. None studied were over 6 years of age.

Immunization was carried out with a toxin-antitoxin mixture and was done on a total of 252 children who had positive Schick tests. These children were then retested by Schick tests at monthly intervals thereafter and the following results were observed:

	Time Interval after Injection	Number Tested	Results		Per Cent. Negative
			Positive	Negative	
Group 1.	3 to 4 months	252	68	184	73
Group 2.	9 to 10 months	130	12	118	91
Group 3.	22 months	50	0	50	100

(The decreasing numbers represent children leaving the institution over the course of the study).

Most significantly, there were no observed diphtheria cases among any of the immunized subjects over the subsequent five years.—Julius Blum, MD, New York (20:22-28, July 1920).

Infants Potentially at Risk for Congenital Toxoplasmosis

A Prospective Study

Babill Stray-Pedersen, MD

• **Fifty-two children were selected as being potentially at risk for congenital toxoplasmosis by serologic testing of 8,043 pregnant women in the Oslo area. These infants were then studied during the neonatal period and subsequently followed up for three years. Three were found to be congenitally infected with *Toxoplasma gondii*, and one infant was dysmature at birth. The diagnosis was confirmed by persistent dye-test antibodies and by recovery of parasites in placenta and/or amniotic fluid. The *Toxoplasma* indirect fluorescent IgM-antibody test remained negative, while measurements of cord IgM and IgA levels and serial estimations of specific antibody load supported an early diagnosis. The specific cell-mediated immunity, as measured by the in vitro lymphocyte stimulation test, turned positive at 1 year of age and then increased markedly during the second and third years. The lymphocyte responses of the uninfected children, however, remained negative. The infected children received pyrimethamine/sulfadiazine treatment during their first year, with no clinical signs of congenital toxoplasmosis.**

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It has been recognized for years that the parasite *Toxoplasma gondii* may cause congenital infection[1] with the classical tetrade of clinical manifestations including chorioretinitis, hydrocephalus, convulsions, and intracerebral calcifications.[2] Recent investigations have shown that in many congenitally infected children, these characteristic symptoms may be partially lacking or absent at birth.[3,4]

The neonates with clinically apparent disease have a poor prognosis; mortality is high and they often show mental retardation and multiple organ involvement.[5] The neonates with inapparent congenital infections, however, may remain asymptomatic for months or years, but subsequently the disease may manifest itself in symptoms involving the brain or the eye.[6-8] Damage caused by the parasites, especially in children with silent infections, may perhaps be prevented if specific treatment is given immediately after birth.[3,4,9] Consequently, the diagnosis should be established as early as possible in the neonatal period.

For editorial comment see p 635.

The incidence of congenital *Toxoplasma* infections in Norway might be expected to be 1 to 2/1,000, according to prevalence studies of acquired infections.[10,11] To study the actual risk of congenital toxoplasmosis in our country, 8,043 pregnant women were screened for *Toxoplasma* antibodies.[1] This article presents the results obtained in a three-year follow-up study of 52 children delivered in pregnancies potentially at risk for congenital transmission.

SUBJECTS AND METHODS

Subjects

The study included 52 infants identified in a prospective screening based on serologic examination (dye test and indirect fluorescent IgM-antibody test [IgM-IFAT]) of 8,043 paired blood samples from pregnant women in the Oslo area during the years 1974 and 1975.[12] The infants were divided into three risk groups according to the approximate time of the maternal infection.

Group 1 (high risk) consisted of 11 children (patients 1 through 8 and 11 through 13) whose mothers acquired the infection during pregnancy. The dye test in eight of these mothers (of patients 1 through 8) had converted from negative to positive; one mother (of patient 11) had shown a substantial rise in dye-test titer; and two mothers (of patients 12 and 13) had high titers (≥ 300 IU/mL). Ten of the 11 women had a positive IgM-IFAT during pregnancy.

Group 2 (minor risk) included 18 infants whose mothers acquired the infection shortly before conception. In seven mothers, the dye-test titer was high, but the IgM-IFAT was negative in the first trimester; in the remaining 11 mothers, the dye-test titer was moderately high (100 to

300 IU/mL) and the IgM-IFAT was positive in the first half of pregnancy.

Group 3 (minimal risk) comprised 23 children whose mothers' infections were acquired months before conception. The dye-test titer of these mothers was moderately high, and the IgM-IFAT was negative throughout the gestational period.

Study Protocol

Amniotic fluid, placenta and umbilical cord tissue, and cord blood were obtained at delivery, and the infants were observed in the nursery for at least eight days during which serologic, clinical, ophthalmoscopic, and radiologic examinations were performed. The infants in group 1 were similarly examined at 6, 12, and 24 months of age, and motor and mental development was assessed at 36 months of age. Blood samples were drawn monthly from all of the children during the first six months of life, then every third month until 18 months of age. Thereafter, serum samples were collected annually from group 1 infants. These infants are still being followed up.

Treatment

All neonates in group 1 received daily doses of spiramycin (Rovamycin [Great Britain]; no comparable US product), 50 mg/kg/24 hr, for three weeks. When evidence of congenital infection was obtained, a three-week course of pyrimethamine (Daraprim), 1 mg/kg/24 hr, sulfadiazine, 50 mg/kg/24 hr, and folic acid, 0.1 mg/kg/24 hr, was given; this regimen was repeated twice during the first year of life (Figure). The infant received one daily oral dose of a powder mixture of the drugs. This was administered at home under the supervision of a pediatric clinic. During the pyrimethamine treatment, weekly blood cell and platelet counts were performed.

Laboratory Tests

The blood samples were always examined together with specimens previously collected from the infant and the mother and stored at −20 °C.

For the dye test (DT), a micromodification of the classic Sabin-Feldman method was used,[11] and the results were expressed in reference to the international standard for anti-*Toxoplasma* serum. Serum samples with less than 5 IU/mL were considered negative.

The IgM-IFAT was employed as described by Remington et al,[13] using fluorescein conjugated antihuman IgM specific for μ-chain (Dakopatts A/S, Denmark).

Serum IgM, IgA, and IgG levels and C-reactive protein concentrations were measured by single radial diffusion, employing commercially available antibody agar plates.

Specific antibody load was defined as the number of international units of *Toxoplasma* antibodies per milligram of IgG.[14] The value was estimated separately for each serum sample.

The cell-mediated immunity (CMI) was measured with use of a micromodification of the in vitro lymphocyte stimulation test (LST), with a lysate of *T gondii* (32 μg/mL of protein) as antigen.[15] The mononuclear cells were isolated from heparinized blood samples by centrifugation and cultured in medium RPMI 1640 containing 20% pooled human AB serum. Cultures containing 250,000 cells and 250 μL of medium were stimulated by 10 μL of antigen and treated as previously described.[16] Harvesting was performed on the sixth day with fiberglass filters. The incorporation of tritiated thymidine, which had been added 18 hours before the harvest, was measured by a liquid scintillation counter. A positive control was included in every test run, as well as control cultures without antigen. The degree of stimulation (stimulation index [SI]) was given as the ratio between the increment in counts per minute in the stimulated culture and the cpm in the unstimulated culture. An SI greater than 2 was considered positive.

Demonstration of Parasites

Amniotic fluid, cord blood, cord tissue, and placental tissue were examined for parasites. Amniotic fluid was centrifuged at low speed and the supernatant was used. Cord blood was allowed to clot. Placental tissue (50 g) was homogenized in a mortar with the addition of 2 mL of sterile isotonic saline solution containing 100 IU/mL of penicillin and 100 μg/mL of streptomycin per gram. Drop preparations were made for microscopical examinations. For animal inoculation, the placental tissue was digested with a solution containing 0.25 g trypsin.[17]

The indirect fluorescent antibody test for detection of parasites was performed as described earlier.[18] Approximately ten drop-preparations from each sample were studied. The test was considered positive if at least three parasites were observed in each preparation of the sample.

Animal Inoculation

The test suspensions (supernatant of the amniotic fluid, digested placental homogenate, cord blood clot) were mixed with penicillin, 100 IU/mL, and streptomycin, 100 μg/mL; 0.5 mL was injected intraperitoneally into five DT-negative female mice. After six weeks, the mice were bled and killed. A DT was performed and suspensions of brain were examined microscopically for cysts.

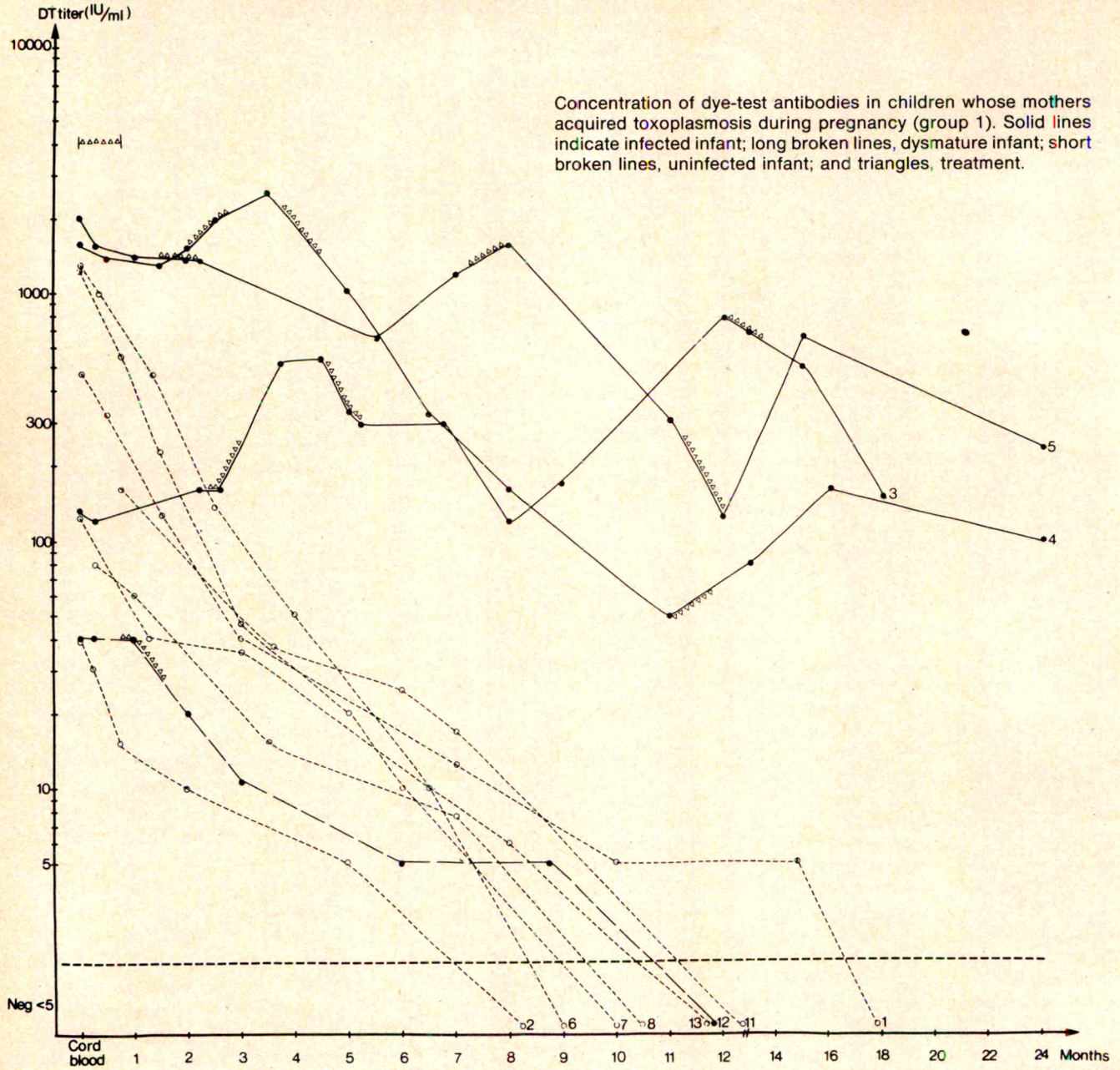
RESULTS

Neonatal Evaluation

Clinical Examinations.—The deliveries of the 52 children were normal and occurred approximately at term. One child (patient 12) was born dysmature, weighing 2,130 g after 40 weeks' gestation. Weights of the other infants were within normal range (means, 3,540 g in group 1, 3,600 g in group 2, and 3,580 g in group 3). Head circumferences were within normal limits (35 ± 2 cm), and Apgar scores recorded one minute after delivery were in all cases 7 or greater. In the neonatal period, hepatosplenomegaly was observed in one infant (patient 5), and another (patient 2) showed hyperbilirubinemia and icterus. Funduscopic examinations of the neonates demonstrated no eye abnormalities, and roentgenograms did not show intracerebral calcifications or other abnormalities of the skull.

Serologic Tests.—The concentrations of DT antibodies in cord blood ranged from 40 to 2,050 IU/mL in group 1 (Figure). Four children (patients 4 through 7) had titers above 1,000 IU/mL. The levels of groups 2 and 3, however, were within the range of 40 to 420 IU/mL. The titers were almost identical to maternal values except in those infants in group 1 whose mothers were in the acute stage of infection at the time of delivery (DT > 300 IU/mL; IgM-IFAT, positive). The IgM-IFAT was negative in all samples of cord blood. The concentration of cord IgM, however, was found to be elevated in three children of group 1 (patients 1 and 4, 0.23 mg/mL; patient 5, 0.49 mg/mL), while the mean values of the remaining children in group 1 and the children in the two other groups were 0.15 mg/mL. The concentrations of the cord IgA were, in most cases, unmeasurable (ie, < 0.01 mg/mL). One infant (patient 4), however, had a value of 0.07 mg/mL.

Parasite Identification.—In three infants (patients 3, 4, and 5), parasites could be demonstrated in the amniotic fluid and/or the placental tissue; thus,



Concentration of dye-test antibodies in children whose mothers acquired toxoplasmosis during pregnancy (group 1). Solid lines indicate infected infant; long broken lines, dysmature infant; short broken lines, uninfected infant; and triangles, treatment.

these three children were unequivocally infected with *T gondii* in utero. In infants 3 and 5, the placentas were found to contain parasites both by inoculation and by immunofluorescence; in infants 4 and 5, the amniotic fluid was parasite-positive by inoculation. In the samples of cord blood and umbilical cord tissue, however, parasites could not be demonstrated. In every case, the amniotic fluid contained DT antibodies, but in much smaller concentrations (range, 10 to 150 IU/mL) than in the cord blood. No IgM-IFAT antibodies were detected in the amniotic fluid.

Treatment.—The prophylactic treatment with spiramycin during the neonatal period was well tolerated, with no adverse effects noted. The three definitely infected infants and one infant (patient 12) with a suspected infection, which later could not be confirmed, received treatment with pyrimethamine, sulfadiazine, and folic acid (Figure). The children tolerated the drugs well. The weekly monitoring of blood cell and platelet counts gave no indication of bone marrow depression.

Long-term Evaluation

Clinical Examinations.—None of the children had clinical manifestations (neural, ocular, cerebral) of congenital toxoplasmosis. The motor and mental development in the three infected children appeared to be normal, but two of them (patients 4 and 5) have

had febrile convulsions, but with normal electroencephalograms.

Serologic Tests.—The serum DT levels measured during the first two years in group 1 infants are shown in the Figure. The amount of DT antibodies in the neonatal period was lower than in cord blood. In the dysmature infant (patient 12), however, the DT titer remained elevated in the blood samples collected during the first month after delivery. In the uninfected children, the titers then decreased exponentially, showing a reduction of about 50% per month, and becoming negative usually between 8 and 18 months of life. In the three infected infants, the *Toxoplasma* antibodies persisted and a DT concentration of 150 to 300 IU/mL was measured at the age of 2 years.

The IgM-IFAT remained negative in all infants. One of the infected children (patient 5) had excessive IgM production during his first year, while the synthesis of IgM and IgA of the two others did not differ from that of the uninfected children. As expected, the IgG concentration decreased markedly after birth, reaching minimum levels before 6 months of age, then showing a steady increase. Consequently, the specific antibody load was found to increase in the postnatal period in the three infected infants and in the dysmature infant (patient 12). In the former, the values thereafter remained unabated, while the latter infant's antibody load decreased rapidly in similarity to that observed in the uninfected children.

Cell-Mediated Immunity.—The specific CMI was found to be negative (SI, < 2) in samples obtained from two of the infected infants (patients 3 and 5) during their first year. (Patient 4 was also tested, but the results were discarded because of technical difficulties.) At 12 months of age, the responses in all three infected children were weakly positive (SI, 3 to 4). Thereafter, the stimulation increased markedly, giving SI values between ten and 45 during the second and third years. Among the repeatedly tested uninfected infants, one child showed a weakly positive LST response (SI, 2) at 1½ years of age, while the other children remained LST-negative.[15]

COMMENT

Children in all of the risk groups developed normally throughout the period of observation, and no clinical manifestations of congenital toxoplasmosis were observed. The serologic follow-up examinations, however, showed that three children had been infected, and the diagnosis was confirmed by recovery of parasites from either the placenta or the amniotic fluid. The fact that these three children all belonged to group 1 strongly supports the generally accepted theory that congenital toxoplasmosis occurs only in those pregnancies in which the woman acquires the infection during her gestational period.[14]

The serologic examinations of cord blood appeared to be of less value in determining the diagnosis. The presence of specific IgM antibodies represents a reliable indicator of congenital toxoplasmosis,[4,19] but in the present study the *Toxoplasma* IgM-IFAT was negative in the cord blood as well as in the subsequent blood samples from the infected children. This lack of diagnostic sensitivity has also been reported in other investigations.[14,20] Quantitative determinations of cord IgM and IgA levels have been proposed as an alternative method in screenings of congenital toxoplasmosis,[4,21] and in two of the infected infants, the cord concentrations of these immunoglobulins were found to be elevated.

The DT titers of the uninfected children decreased gradually by age and became negative between 8 and 18 months of age, depending on the cord DT level (Figure). The reduction in titers corresponded to the expected rate of decline of maternal antibodies in the infant. In the infected children, the concentration of DT antibodies showed a transient minor decrease and then remained elevated throughout the period of observation. On the basis of the DT curves, therefore, the diagnosis became evident between one and three months after the delivery. At an earlier stage, ie, during the first postnatal weeks, estimations of the specific antibody load suggested the diagnosis.

Whereas the immune response to *T gondii* is both humoral and cell mediated, CMI is not transferred from mother to fetus during pregnancy. Hence, demonstration of cellular immunity might serve as a supplementary diagnostic test of congenital infection. In the present study, only the infected infants were strongly positive in the in vitro lymphocyte stimulation test. However, since the development of the CMI became evident after a lag period of several months—a phenomenon that is also observed in adults with acquired toxoplasmosis—a negative test during the first year may not exclude the diagnosis, while a positive test may be indicative.

Child 12 actually represented a diagnostic problem. She was born dysmature; in the neonatal period, the DT titers were stable and the antibody load increased. Thereafter, a marked decrease in the DT titer and the antibody load were observed. No parasites were demonstrated and the CMI remained negative. It is possible that the mother had been infected during the first trimester, and that the maternal infection affected placental development and function, resulting in inadequate fetal growth.

We thought that all infants in the high-risk group required prophylactic therapy (spiramycin). No adverse effects were observed, and the treatment did not seem to influence seroreactivity. In the infected infants, pyrimethamine/sulfadiazine treatment was started as soon as the diagnosis was established. This treatment did not appear to alter the immune responses, as judged by the DT curves and the development of CMI. None of these children had clinical symptoms of congenital toxoplasmosis.

It is of particular note that parasites could be recovered not only from the placenta, as previously reported,[3,22] but also from the amniotic fluid. This finding may provide a future method of diagnosis, even *ante*natally. In suspected cases, amniocentesis might be performed and the fluid examined for content of *T gondii*.

The Department of Pediatrics, Rikshospitalet, University of Oslo, assisted in various ways with this study.

References

1. Wolf A, Cowen D, Paige B: Human toxoplasmosis (occurrence in infants as an encephalomyelitis: Verification by transmission to animals). *Science* 89:226-227, 1939.

2. Sabin AB: Toxoplasmosis, in DeSanctis AG (ed): *Advances in Pediatrics*. New York, Interscience Publishers Inc, 1942, pp 1-56.

3. Desmonts G, Couvreur J: Congenital toxoplasmosis. *N Engl J Med* 290:1110-1116, 1974.

4. Alford CA, Stagno S, Reynolds DW: Toxoplasmosis: Silent congenital infection, in Krugman S, Gershon AA (eds): *Infections of the Fetus and the Newborn Infant*. New York, Alan R Liss, 1975, pp 133-157.

5. Eichenwald HF: A study of congenital toxoplasmosis, in Siim JC (ed), *Human Toxoplasmosis*. Copenhagen, Munksgaard, 1960, pp 41-49.

6. Couvreur J, Desmonts G: Congenital and maternal toxoplasmosis: A review of 300 congenital cases. *Dev Med Child Neurol* 4:519-530, 1962.

7. Thalhammer O: Prevention of congenital toxoplasmosis. *Neuropaediatrie* 43:233-237, 1973.

8. Stagno S, Reynolds DW, Amos CS, et al: Auditory and visual defects resulting from symptomatic and subclinical congenital cytomegaloviral and *Toxoplasma* infections. *Pediatrics* 59:669-678, 1977.

9. Saxon SA, Knight W, Reynolds DW, et al: Intellectual deficits in children born with subclinical congenital toxoplasmosis. *J Pediatr* 82:792-797, 1973.

10. Stray-Pedersen B, Pedersen JO, Omland T: Estimations of incidences of *Toxoplasma* infections among pregnant women from different areas in Norway. *Scand J Infect Dis* 11:247-252, 1979.

11. Stray-Pedersen B, Lorentzen-Styr AM: The prevalence of *Toxoplasma* antibodies among 11,736 pregnant women in Norway. *Scand J Infect Dis* 11:159-165, 1979.

12. Stray-Pedersen B: A prospective study of acquired toxoplasmosis among 8,043 pregnant women in the Oslo area. *Am J Gynecol Obstet* 136:399-406, 1980.

13. Remington JS, Miller MJ, Brownlee I: IgM antibodies in acute toxoplasmosis: II. Prevalence and significance in acquired cases. *J Lab Clin Med* 71:855-866, 1968.

14. Remington JS, Desmonts G: Toxoplasmosis, in Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, WB Saunders Co, 1976, pp 191-332.

15. Closs O, Stray-Pedersen B: In vitro lymphocyte stimulation with specific antigen in congenital toxoplasmosis. *Scand J Infect Dis*, to be published.

16. Closs O: In vitro lymphocyte response to purified protein derivate BCG, and *Mycobacterium leprae* in a population not exposed to leprosy. *Infect Immun* 11:1163-1169, 1975.

17. Desmonts G, Couvreur J: L'isolement du parasite dans la toxoplasmose congenitale. *Arch Fr Pediatr* 31:157-166, 1974.

18. Stray-Pedersen B, Lorentzen-Styr AM: Uterine *Toxoplasma* infection and repeated abortions. *Am J Obstet Gynecol* 128:716-721, 1977.

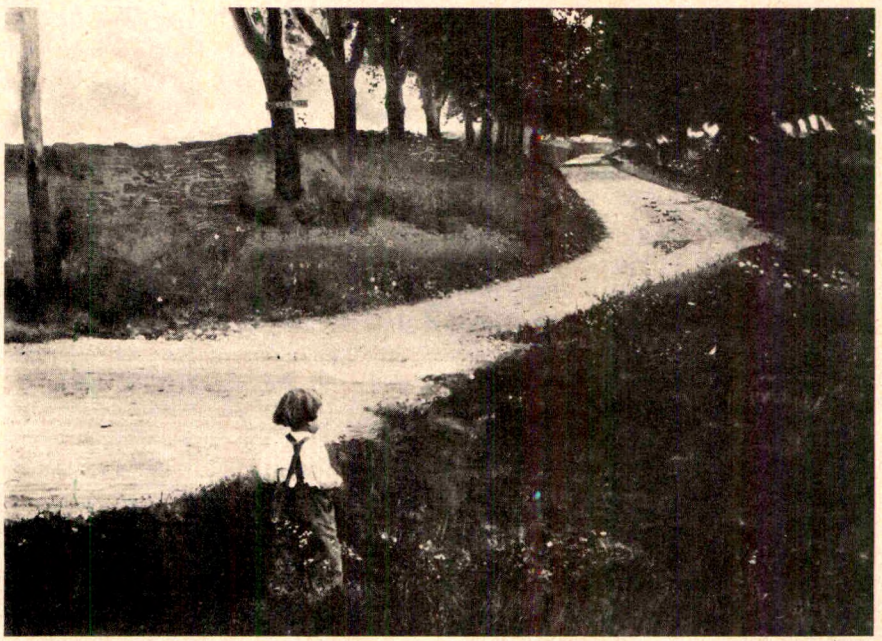
19. Werner H, Schöning C, Neuhaus B, et al: Interpretation des Nachweises spezifischer IgM-Antikörper bei Verdacht auf connatale Toxoplasmose. *Z Geburtshilfe Perinatol* 180:438-444, 1976.

20. Remington JS, Desmonts G: Congenital toxoplasmosis: Variability in the IgM-fluorescent antibody response and some pitfalls in diagnosis. *J Pediatr* 83:27-30, 1973.

21. Cederquist LL, Kimball AC, Ewool LC, et al: Fetal immune response following congenital toxoplasmosis. *Obstet Gynecol* 50:200-204, 1977.

22. Kimball AC, Kean BH, Fuchs F: Congenital toxoplasmosis: A prospective study of 4,048 obstetric patients. *Am J Obstet Gynecol* 111:211-218, 1971.

Road to Rome



Gertrude Käsebier 1902 From the International Museum of Photography, Rochester, NY

Chemoprophylaxis for *Pneumocystis carinii* Pneumonitis

Outcome of Unstructured Delivery

Richard B. Wilber, MD; Sandor Feldman, MD; William J. Malone, MD; Michael Ryan, DO; Rhomes J. A. Aur, MD; Walter T. Hughes, MD

• **Sulfamethoxazole-trimethoprim was administered prophylactically to 786 patients judged to be at sufficient risk for development of *Pneumocystis carinii* pneumonitis. The selection of patients, administration of the agents, and surveillance for compliance were the responsibility of the attending oncologists rather than specialists in infectious diseases, as in an earlier trial at this center. The recommended dosage was trimethoprim, 150 mg/sq m/day, and sulfamethoxazole, 750 mg/sq m/day. Over a three-year study period, nine cases of *P carinii* pneumonitis occurred at this institution, with none attributable to drug failure. Adverse reactions, skin rashes mainly, were noted in 43 patients, and one patient died with Stevens-Johnson syndrome. These results confirm the efficacy of sulfamethoxazole-trimethoprim in preventing *P carinii* pneumonitis in childhood cancer patients and illustrate the feasibility of large-scale unstructured delivery of the combination to patients with malignant diseases frequently associated with this pneumonia.**
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Prophylactic use of antimicrobial agents has been a persistently appealing, though seldom successful, strategem for the prevention of infectious diseases.[1] Hughes et al,[2] however, have shown that sulfamethoxazole-trimethoprim is highly effective in the prevention of *Pneumocystis carinii* pneumonitis. In their double-blind placebo-controlled trial conducted at this center for patients at high risk for *P carinii* pneumonitis, a closely supervised, structured system of drug delivery was used, with a full-time monitor to ensure patient compliance and verification of drug-induced adverse reactions. Patients received the drug continuously throughout the duration of anticancer therapy. Dosages were trimethoprim, 150 mg/sq m/day, and sulfamethoxazole, 750 mg/sq m/day, given in two divided doses. Recently, Harris et al[3] have confirmed the efficacy of sulfamethoxazole-trimethoprim prophylaxis administered according to a similar regimen.

Even when a drug is proved effective for prophylaxis, its delivery by the physician and acceptance by the patient may be inadequate. Thus, despite the known value of sulfamethoxazole-trimethoprim prophylaxis, a pragmatic question remained: what impact would use of this drug combination have on the overall incidence of *P carinii* pneumonitis when patient selection, drug administration, and surveillance of compliance were the responsibility not of a full-time monitor but of the attending oncologist and the patient or parent, as would be the case in most settings other than a cancer research treatment center? Accordingly, an open study with an unstructured delivery system (ie, no full-time monitor) was undertaken to evaluate the effect of these variations in protocol design. A second purpose of the study was to provide a means for the possible elimination of this disease in our patient population.

SUBJECTS AND METHODS

Selection of Patients and Calculation of Risk

From November 1976 through December 1979, sulfamethoxazole-trimethoprim was administered to all patients at St Jude Children's Research Hospital who, in the judgment of the attending oncologists, were at sufficient risk for *P carinii* pneumonitis. Data on which to base this judgment were provided at the outset of the study by the Infectious Diseases Service. Projected risk was based on retrospective assessment of the incidence of *P carinii* pneumonitis in this institution as a whole, and within specific tumor and therapy groups during the years 1970 through 1975, ie, before the general use of sulfamethoxazole-trimethoprim prophylaxis. Previously published and unpublished studies had

related the risk of *P carinii* pneumonitis at this institution to both the type of malignancy and the intensity of administered chemotherapy.[4] However, in determining the population at risk for *P carinii* pneumonitis, ie, those eligible to receive sulfamethoxazole-trimethoprim, the intensity of administered drug therapy was not considered. All patients whose tumor types had been associated with *P carinii* pneumonitis at this center were included in the population at risk and were eligible for sulfamethoxazole-trimethoprim prophylaxis during their anticancer therapy.

Annual institutional attack rates for *P carinii* pneumonitis were calculated by dividing the number of cases in a given year by the number of patients who had only those tumor types and who had attended the hospital in that year. *Pneumocystis carinii* pneumonitis-associated tumor types and attack rates for the years immediately prior to this study are given in Table 1. This method results in a broad population base and includes patients with varying risk for *P carinii* pneumonitis, but it provides the benefit of prophylaxis to all who may be at risk as well as the most consistent inclusive population in which to analyze the year to year changes in the overall institutional incidence of *P carinii* pneumonitis.

Drug Administration and Monitoring

Informed consent was obtained for all patients who received prophylaxis. The recommended dosage was trimethoprim, 150 mg/sq m/day, and sulfamethoxazole, 750 mg/sq m/day. The combination was administered orally in tablet or suspension form in two equal doses given at 12-hour intervals. No more than 320 mg of trimethoprim and 1.6 g of sulfamethoxazole were given in any 24-hour period. Each tablet contained 80 mg of trimethoprim and 400 mg of sulfamethoxazole. The suspension contained 40 mg of trimethoprim and 200 mg of sulfamethoxazole per 5.0 mL. Since in the successful preceding structured study, prophylaxis was given continuously throughout anticancer therapy, this approach was also recommended for the current study. Termination of prophylaxis was advised only for unacceptable adverse reactions, onset of *P carinii* pneumonitis while receiving sulfamethoxazole-trimethoprim prophylaxis, or after completion of one month of prophylaxis following successful termination of anticancer chemotherapy. Records of sulfamethoxazole-trimethoprim dispensed to patients were maintained in the computer files of the hospital pharmacy.

The absence in the previous structured study of any noticeable effect on the recipients' tolerance for anticancer chemotherapy indicated that planned modification of chemotherapy would not be necessary. Also, in view of the low anticipated rate of adverse reactions and since this was a study of an "unstructured" delivery system, reporting of side effects depended on the assessment by the attending oncologist of the relationship of the reaction to sulfamethoxazole-trimethoprim and its importance. These side effects were identified at the completion of the study by a computer-assisted search of the medical records for any side effects attributed to sulfamethoxazole-trimethoprim.

Table 1.—Annual Attack Rates of *Pneumocystis carinii* Pneumonitis by Category of Malignancy*

	No. (%) of Cases/No. of Patients at Risk					
Malignancy	**1975**	**1974**	**1973**	**1972**	**1971**	**1970**
Leukemia	26/405 (6)	31/370 (8)	24/328 (7)	12/297 (4)	12/263 (5)	18/211 (9)
Ewing's sarcoma	1/33 (3)	0/24 (0)	0/17 (0)	0/18 (0)	0/13 (0)	0/9 (0)
Hodgkin's disease	2/117 (2)	0/101 (0)	0/81 (0)	0/73 (0)	0/54 (0)	0/44 (0)
Neuroblastoma	1/61 (2)	1/48 (2)	0/32 (0)	1/33 (3)	1/28 (4)	0/17 (0)
Rhabdomyosarcoma	3/47 (6)	2/29 (7)	0/28 (0)	0/25 (0)	0/16 (0)	0/14 (0)
Wilms' tumor	0/60 (0)	1/46 (2)	0/44 (0)	0/43 (0)	0/35 (0)	0/33 (0)
Histiocytosis	2/21 (10)	0/20 (0)	0/16 (0)	0/12 (0)	0/18 (0)	0/13 (0)
Lymphomas	2/53 (4)	4/39 (10)	1/29 (3)	1/27 (3)	0/25 (0)	1/16 (6)
Total	**37/797 (5)**	**39/677 (6)**	**25/575 (4)**	**14/528 (3)**	**13/452 (3)**	**19/357 (5)**

*Data provided to attending physician.

Identification and Management of Patients With *P carinii* Pneumonitis

The diagnosis of *P carinii* pneumonitis was made only when typical *P carinii* organisms were identified by either Gomori's methenamine silver nitrate or toluidine blue-0 staining of pulmonary aspirates or lung specimens obtained before or after death. Since the mortality of untreated *P carinii* pneumonitis is about 100% in immunosuppressed patients,[5] cases not recognized clinically were expected to be detected by autopsy studies. The clinical management of those cases of *P carinii* pneumonitis that occurred during the study followed previously published guidelines,[6] and in those cases the choice of pentamidine or sulfamethoxazole-trimethoprim for antipneumocystis therapy was determined by best clinical management.

Evaluation of Prophylaxis Success

Comparison of annual attack rates of *P carinii* pneumonitis at this center prior to and after initiation of this study were used to measure the success of this method of delivery and to judge whether the goal of the study, elimination of *P carinii* pneumonitis as a cause of morbidity and mortality in patients at this center, was realized. Each case of the pneumonia was considered a failure of prophylaxis. Failures were attributed either to drug inefficacy if *P carinii* pneumonitis developed while receiving the recommended dose of sulfamethoxazole-trimethoprim, or to inadequate drug delivery if the patient was not receiving the combination or was receiving a lower than recommended dosage.

RESULTS

Patients Chosen to Receive Prophylaxis

Each year during the study period, roughly 1,000 patients per year were determined to be at risk for *P carinii* pneumonitis, based on previous association of their tumor type with *P carinii* pneumonitis. Of these patients, those not chosen to receive prophylaxis were judged to be at too low a risk by the attending oncologists, who considered the intensity of administered therapy, the age of the patient, and the phase of therapy as well as *P carinii* pneumonitis-associated tumor types to be important determinants of risk. With these combined criteria for risk, the oncologists entered 786 patients in the study from

November 1976 through December 1979. Of these patients, not all were given prophylaxis throughout the duration of their chemotherapy. Some received prophylaxis only during phases of therapy associated with a perceived high risk for *P carinii* pneumonitis.

The majority of the patients who received prophylaxis (618/786) had acute leukemia. With the exception of 201 of these who were initially treated in the Total Therapy for Acute Childhood Lymphocytic Leukemia Study IX (the Total IX study) (unpublished study, 1979, R. J. A. Aur, MD, M. S. Verzosa, MD, H. O. Hustu, MD, J. V. Simone, MD), patients with acute leukemia entered in this study received sulfamethoxazole-trimethoprim continuously during chemotherapy. Those in the Total IX study received prophylaxis only during a five- to seven-month period after diagnosis and initiation of therapy. This time was perceived to be an especially high-risk period because, prior to availability of sulfamethoxazole-trimethoprim, six of the first 92 patients in the Total IX study had *P carinii* pneumonitis within three months of diagnosis.[7]

Continuation phase therapy with mercaptopurine daily and methotrexate weekly had been previously associated with about a 2% risk for *P carinii* pneumonitis.[4] For patients treated according to the Total IX study regimen, prophylaxis was discontinued after three to five months of continuation phase therapy because of low perceived risk. Treatment with sulfamethoxazole-trimethoprim was reinstituted only if therapy was intensified because of relapse of their leukemia. This practice was modified in January 1979. After that time, new patients entered into the Total IX study received sulfamethoxazole-trimethoprim continuously, and prophylaxis was reinstituted for those Total IX study patients who were still receiving continuation therapy. The rationale for this change will be mentioned in the "Comment" section.

Patients who entered this study with malignancies other than leukemia also received sulfamethoxazole-trimethoprim continuously during chemotherapy, with the exception of patients with neuroblastoma. They received sulfamethoxazole-trimethoprim only if they were less than 1 year of age, a period of perceived high risk for these patients.

Frequency of *P carinii* Pneumonitis

Despite a continued increase in the number of patients at risk, the annual rate of *P carinii* pneumonitis at this center decreased during this study (Figure). In 1977, three cases of *P carinii* pneumonitis developed among 994 patients (0.3%) at risk. In 1978, five cases of *P carinii* pneumonitis occurred among the 1,120 patients who formed the population at risk (0.45%); in 1979, one case occurred among 1,200 patients (0.08%) considered to be at risk.

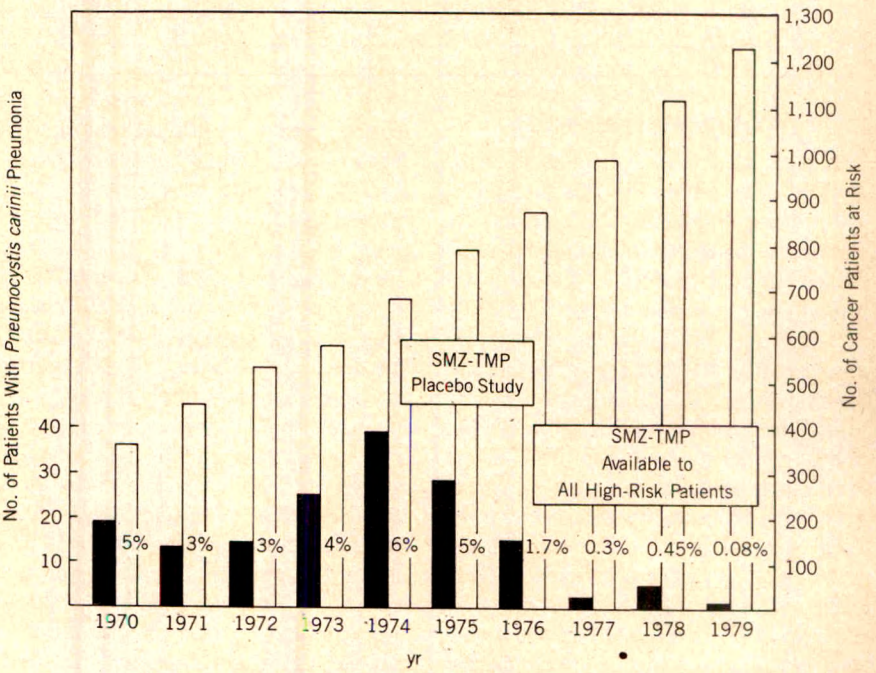
The clinical details of cases of *P carinii* pneumonitis that developed during this study are summarized in Table 2. All subjects except patient 1 were in remission from their primary disease when pneumonitis developed. The case fatality rate remained at about 20% (2/9).

No cases of *P carinii* pneumonitis were discovered at autopsy that had not been apparent before death. During the course of this study, from November 1976 through December 1979, a total of 433 patients at this center died; of this number, 215 (50%) had autopsies. Within the subpopulation of 786 patients entered in this study, 253 died and 128 (51%) had autopsies. Only case 2 (Table 2) had histologic evidence of *P carinii* pneumonitis at autopsy.

Categorization of Failures of Prophylaxis

None of these nine cases could be attributed to the inefficacy of sulfamethoxazole-trimethoprim, as they developed when patients either were not receiving the combination or, as in case 1, were receiving a presumably inadequate dose and hence were considered the result of failure of drug delivery.

No cases occurred in patients excluded from our defined population at risk, ie, in noncancer patients or in patients whose tumor types had not been previously associated with *P carinii* pneumonitis.



Impact of sulfamethoxazole-trimethoprim (SMZ-TMP) prophylaxis on incidence of *Pneumocystis carinii* pneumonitis at St Jude Children's Research Hospital, Memphis. Open bars represent number of active patients at risk with eligible tumor type who attended hospital each year; solid bars denote patients who acquired *P carinii* pneumonitis. Scale for solid bars is ten times as great as for open bars. Availability of chemoprophylaxis for all patients at risk did not begin until November 1976.

Table 2.—Clinical Summary of Cases of *Pneumocystis carinii* Pnemonitis

Patient/ Diagnosis	Age/Sex	Average Daily Dose of Sulfamethoxazole-trimethoprim, mg/sq m	Duration of Prophylaxis, mo	Interval From Last Dose to Diagnosis of *P carinii* Pneumonitis, mo	Anti-*Pneumocystis carinii* Pneumonitis Therapy*	Outcome
1/ALL†	5 yr 9 mo/M	530-106	1½	Was receiving sulfamethoxazole-trimethoprim at diagnosis	Pentamidine, 11 days	Died; no *P carinii* pneumonitis at autopsy
2/ALL‡	4 mo/M	...	...	...	Sulfamethoxazole-trimethoprim, 4 days; pentamidine, 2 days	Died; *P carinii pneumonitis* at autopsy§
3/ALL‡	5 yr 8 mo/M	...	...	...	Sulfamethoxazole-trimethoprim, 4 days; pentamidine, 14 days	Survived
4/ALL	5 yr 9 mo/M	515-103	6	4½	Pentamidine, 12 days	Survived
5/ALL	3 yr 5 mo/M	1,210-242	7	7½	Pentamidine, 14 days	Survived
6/ALL	16 yr/M	800-160	5	3¾	Sulfamethoxazole-trimethoprim, 14 days	Survived
7/NHL‖	13 yr 9 mo/M	850-170	11½	7¼	Pentamidine, 14 days	Survived
8/ALL	3 yr 11 mo/M	600-120	5	4½	Sulfamethoxazole-trimethoprim, 14 days	Survived
9/ALL	6 yr 3 mo/F	800-160	4	4½	Sulfamethoxazole-trimethoprim, 14 days	Survived

*Pentamidine, 4 mg/kg/24 hr, or trimethoprim, 20 mg/kg, and sulfamethoxazole, 100 mg/kg/24 hr.
†Acute lymphocytic leukemia.
‡Did not receive prophylaxis.
§Histopathologic evidence of *P carinii* pneumonitis.
‖Non-Hodgkin's lymphoma.

Table 3.—'Drug Related' Adverse Reactions in 786 Patients

Type of Reaction	No. of Patients	No. of Fatalities
Dermatologic		
Mild skin rashes	24	0
Erythema multiforme	2	0
Stevens-Johnson syndrome	1	1
Gastrointestinal	2	0
Hematologic	14	0

Adverse Reactions

A review of the medical records of the patients entered in this study for reference to side effects ascribed to sulfamethoxazole-trimethoprim disclosed 43 patients (5.4%) with presumed adverse reactions (Table 3). Twenty-four patients had mild skin rashes, often a pruritic, macular papular rash on the face and upper extremities. The relationship to sulfamethoxazole-trimethoprim administration was unclear, however, as the rash resolved in all but three cases with no recurrence when sulfamethoxazole-trimethoprim was reinstituted. Because of their greater severity, two cases of erythema multiforme and one case of Stevens-Johnson syndrome are tabulated separately. The latter accounted for the only "drug related" fatality (0.12%). Gastrointestinal distress occurred in two patients and was primarily manifested as vomiting after taking sulfamethoxazole-trimethoprim. Hematologic abnormalities, neutropenia and anemia, were related to sulfamethoxazole-trimethoprim administration in 14 patients. The drug therapy was discontinued in all cases. In seven of these 14 cases, drug administration resumed when the patients' neutrophil counts had recovered and no further occurrence of neutropenia was demonstrated. The remaining seven patients had recurrences of either anemia or neutropenia when sulfamethoxazole-trimethoprim was readministered, and use of the drug combination was discontinued. However, one of this latter group had *P carinii* pneumonitis 7¼ months after administration of sulfamethoxazole-trimethoprim was stopped. After recovery from *P carinii* pneumonitis, sulfamethoxazole-trimethoprim was reinstituted simultaneously with leucovorin. He tolerated this regimen without further anemia or neutropenia.

COMMENT

The outcome of this study confirms an earlier report of the efficacy of sulfamethoxazole-trimethoprim in the prevention of *P carinii* pneumonitis,[2] and demonstrates the feasibility of large-scale unstructured delivery of prophylaxis to patients in well-defined tumor categories, selected because of their previous association with *P carinii* pneumonitis. The most important factor contributing to the continued decrease in both the absolute number of cases of *P carinii* pneumonitis and in the attack rate (Figure) appears to be the introduction of sulfamethoxazole-trimethoprim prophylaxis. This conclusion and the data on which it is based would be open to question if during this study period we had failed to detect cases of *P carinii* pneumonitis that occurred, or if changes in intensity of chemotherapy administered to the majority of patients had reduced the susceptibility of the population to *P carinii* pneumonitis. With regard to the failure to detect cases of *P carinii* pneumonitis, physicians at this center and cooperating local physicians caring for these patients are familiar with and

alert for the presentation of *P carinii* pneumonitis. No patient at this center receives pentamidine or *therapeutic* (anti-*P carinii* pneumonitis) dosages of sulfamethoxazole-trimethoprim (trimethoprim, 20 mg/kg/day, and sulfamethoxazole, 100 mg/kg/day[6]) for any reason other than an histologically confirmed diagnosis of *P carinii* pneumonitis. If this pneumonia remains untreated in a patient whose immunity is blunted by cancer or anticancer therapy, there is virtually 100% mortality.[5] Therefore, any undetected cases of *P carinii* pneumonitis would be untreated, and would be detected at autopsy, where processing of lung tissue with Gomori's methenamine silver stain was included in the standard autopsy protocol. Although the autopsy rate at this center during this period had declined to approximately 50%, it is unlikely that many cases of this pneumonia were undetected.

The intensity of chemotherapy administered to patients at this center during this study, at least for those patients at highest risk for *P carinii* pneumonitis, ie, those with acute leukemia, was essentially as intensive as that administered during the years 1970 through 1971. During that period, there were fewer patients at risk per year—357 and 452, respectively—and more cases of *P carinii* pneumonitis—18 cases in 1970 and 12 cases in 1971 (Table 1). In light of these considerations, our data indicate that the reduction of both the absolute number of cases and the attack rate of *P carinii* pneumonitis at this center is due primarily to the introduction of sulfamethoxazole-trimethoprim prophylaxis.

In addition to the elimination of *P carinii* pneumonitis among patients at this center, a further objective was to assess the feasibility of an unstructured delivery of prophylaxis, including the designation of an at-risk population based on previous *P carinii* pneumonitis-tumor type association. The fact that no cases occurred outside of the population defined to be at risk and eligible for prophylaxis demonstrates that this is an acceptable method for defining patients at risk, although we realize it does include patients at low risk and we caution that the specific tumor groups defined to be at risk apply only to this center. Physicians at other centers should evaluate the risk of *P carinii* pneumonitis for their patients based on observed frequencies of the disease at their institutions.

The occurrence of nine cases of *P carinii* pneumonitis during the study among patients eligible for prophylaxis prompted examination of these failures of drug delivery. Several explanations for these failures were apparent. As might be expected, occasional eligible patients were inadvertently not entered into this study and thus did not receive sulfamethoxazole-trimethoprim prophylaxis (patient 2 in Table 2). Also, the drug was occasionally prescribed in less than the recommended dosage (patient 1). Some patients had unacceptable adverse reactions, resulting in withdrawal of chemoprophylaxis (patient 7). Patient 3 was receiving antileukemic treatment as specified in Total Therapy Study VIII, group C, in which the calculated risk of pneumonitis was 2.5%.[4] This risk was judged to be insufficient by the attending oncologists, so that this patient did not receive the combination. Analysis of the five remaining cases (patients 4, 5, 6, 8, and 9 in Table 2) showed that they were being treated in the Total IX study, and by design of the attending physicians did not receive sulfamethoxazole-trimethoprim after three to five months of continuation phase therapy (mercaptopurine daily and methotrexate weekly) because in a previous study a similarly treated group[4] had had a ≤2% incidence of *P carinii* pneumonitis during continuation phase therapy. However, 3¾ to 7½ months after sulfamethoxazole-trimethoprim therapy was discontinued, *P carinii* pneumonitis developed in these five patients. This experience closely parallels that of Wolff and Baehner,[8] who used a higher dosage of sulfamethoxazole-trimethoprim for a relatively brief time shortly after induction therapy was begun. Among their patients, *P carinii* pneumonitis occurred 128 to 203 days after prophylaxis was discontinued. Such experience emphasizes the uncertainty of determining what level of risk justifies prophylaxis. However, when the frequency of *P carinii* pneumonitis in a particular tumor or therapy category is low, one must carefully weigh the benefits of possible prevention of the infection against the risk of drug toxicity.

Comparison of the incidence of adverse reactions among patients in this study with that in the general population receiving sulfamethoxazole-trimethoprim is difficult. Our patients received sulfamethoxazole-trimethoprim for up to 30 months as opposed to a standard ten-day course of therapy.[9] Moreover, the few children who have received sulfamethoxazole-trimethoprim for a period comparable to that of our patients[10] have not usually received other drugs simultaneously. Detection of adverse reactions to sulfamethoxazole-trimethoprim during this study depended on the assessment by the attending physician of the relationship of any such occurrences to the drug combination, and thus our data reflect only those reactions noted by the attending physician. Also, as is the practice at this center, patients in this study received care as outpatients as often as possible; in addition, many patients received at least part of their care from closely cooperating physicians based close to the patient's home. Despite these limitations on observation, close follow-up is possible as the patients return quite frequently to this center. Also, frequent telephone communication is maintained with assisting local physicians and uniform records are compiled by having local physicians use and forward copies of patient profile sheets provided by this center. These limitations notwithstanding, the incidence of gastrointestinal, hematologic, and dermatologic drug-related side effects in our study group (5.4%) appears slightly higher than that reported for the general population. The occurrence of one "drug related" fatality among 786 patients (0.12%) is higher than would be expected for the general population, in which drug-related deaths have been as low in frequency as 2.5/100,000 to 1/10,000,000 depending on the source.[11,12] Although this death cannot be unequivocally ascribed to sulfamethoxazole-trimethoprim, the

possibility of lethal toxicity weighs against administration of the combination unless the risk of *P carinii* pneumonitis is sufficient. One must realize, however, that even when this infection is promptly recognized and properly treated, its mortality is usually 20% to 30%.[6]

Results of recent in vitro studies of the effect of sulfamethoxazole-trimethoprim on human bone marrow culture suggest that the antifolate activity of the combination may have been responsible for the neutropenia and anemia that developed in 14 of our patients.[13] One of these patients later received leucovorin along with sulfamethoxazole-trimethoprim. The fact that he was able to maintain acceptable neutrophil counts while receiving both drugs adds further substance to this speculation.

The occurrences of *P carinii* pneumonitis during this study and the study by Wolff and Baehner[8] after cessation of prophylaxis was interesting in view of studies by Hughes et al[14,15] and supports the hypothesis that *P carinii* is highly prevalent as an endogenous agent in man and animals and that sulfamethoxazole-trimethoprim merely suppresses and does not eliminate these organisms from the host. This would explain the recurrence of *P carinii* pneumonitis in the immunosuppressed host after short-term prophylaxis. The results of our clinical study are consistent with these experimental data and provide a compelling argument for continuation of sulfamethoxazole-trimethoprim prophylaxis throughout the duration of anticancer chemotherapy. At this center, those patients in the Total IX study who prior to January 1979 did not receive continuous sulfamethoxazole-trimethoprim now receive prophylaxis, as do other patient groups, until one month after cessation of anticancer therapy.

It is likely that the dosage recommended is adequate but very near the threshold for suppression of this infection since slightly lower doses have been associated with *P carinii* pneumonitis (patient 1). Further prophylaxis regimens may benefit from the recently confirmed in vitro propagation of *P carinii*,[16,17] since this capability could permit in vitro determination of a minimal inhibitory concentration range of sulfamethoxazole-trimethoprim for this organism. Determination of serum levels of the drug combination could then be used to adjust the dose of sulfamethoxazole-trimethoprim during prophylaxis.

This study was not designed to evaluate the effect of sulfamethoxazole-trimethoprim on the frequency of bacterial infections among patients who received prophylaxis. However, in a previous study,[2] there was a statistically significant decrease in bacterial infections among recipients of sulfamethoxazole-trimethoprim as compared with a control group who received a placebo. This antibacterial effect may be considered an additional benefit favoring the use of sulfamethoxazole-trimethoprim prophylaxis in cancer patients.

In summary, after a study period of three years, we conclude that sulfamethoxazole-trimethoprim will effectively prevent *P carinii* pneumonitis if administered in an open unstructured delivery system and if given continuously throughout the course of anticancer therapy. Although the data are applicable only to this institution, the methods for establishing the population of patients at risk, ie, retrospective analysis of *P carinii* pneumonitis-associated tumor types, could be used at other institutions with large numbers of childhood cancer patients. The possibility of severe drug-related toxicity should not take precedence over the risk of *P carinii* pneumonitis, although in patients with erythema multiforme or Stevens-Johnson syndrome, we recommend that sulfamethoxazole-trimethoprim therapy be discontinued.

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Nonproprietary Names and Trademarks of Drug

Sulfamethoxazole-trimethoprim—*Bactrim, Septra.*

References

1. Eichenwald HF, McCracken GH: Antimicrobial therapy of infants and children: I. *J Pediatr* 93:337-355, 1978.

2. Hughes WT, Kuhn S, Chaudhary S, et al: Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 297:1419-1426, 1977.

3. Harris RE, McCallister JA, Sari AA, et al: Prevention of pneumocystis pneumonia. *Am J Dis Child* 134:35-38, 1980.

4. Hughes WT, Feldman S, Aur RJA, et al: Intensity of immunosuppressive therapy and the incidence of *Pneumocystic carinii* pneumonitis. *Cancer* 36:2004-2009, 1975.

5. Hughes WT: *Pneumocystis carinii* pneumonia. *N Engl J Med* 297:1381-1383, 1977.

6. Hughes WT, Feldman S, Chaudhary S et al: Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of *Pneumocystis carinii* pneumonia. *J Pediatr* 92:285, 1978.

7. Feldman S, Wilber R, Hughes WT: Impact of unstructured delivery of chemoprophylaxis for *P carinii* pneumonitis. Read before the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1978, Atlanta.

8. Wolff LJ, Baehner RL: Delayed development of pneumocystis pneumonia following administration of short term high-dose trimethoprimsulfamethoxazole. *Am J Dis Child* 132:525-526, 1978.

9. McCracken GH, Eichenwald HF: Antimicrobial therapy of infants and children: II. *J Pediatr* 93:357-377, 1978.

10. Forbes PA, Drummond KN: Trimethoprim-sulfamethoxazole in recurrent urinary tract infections in children. *J Infect Dis* 128(suppl):626-628, 1973.

11. Havas L, Fernex M, Leonox-Smith I: the clinical efficacy and tolerance of cotrimoxazole (Bactrim, Septrin): An analysis of 37,340 cases. *Clinical Trials J* 10:81-86, 1973.

12. Frisch JM: Clinical experience with adverse reactions to trimethoprim-sulfamethoxazole. *J Infect Dis* 128(suppl):607-611, 1973.

13. Golde DW, Noelle B, Quan SG, et al: Trimethoprim and sulphamethoxazole inhibition of haematopoiesis *in vitro*. *Br J Haematol* 40:363-367, 1978.

14. Hughes WT, McNabb PC, Makres TD, et al: Efficacy of trimethoprim and sulfamethoxazole in the prevention and treatment of *Pneumocystic carinii* pneumonitis. *Antimicrob Agents Chemother* 5:289-293, 1974.

15. Hughes WT: Limited effect of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis on *Pneumocystis carinii*. *Antimicrob Agents Chemother* 16:333-335, 1979.

16. Pifer LL, Hughes WT, Murphy MJ Jr: Propagation of *Pneumocystis carinii in vivo*. *Pediatr Res* 11:305-316, 1977.

17. Barlett MS, Verbanac PA, Smith JW: Cultivation of *Pneumocystis carinii* with WI-38 cells. *J Clin Microbiol* 10:796-799, 1979.

Cleidocranial Dysostosis, Severe Micrognathism, Bilateral Absence of Thumbs and First Metatarsal Bone, and Distal Aphalangia

A New Genetic Syndrome

Emilio Yunis, MD, Humberto Varón, MD

• **Five patients from three families have a new genetic syndrome. The features include cleidocranial dysostosis, bilateral absence of the thumbs and of the distal phalanges of the fingers, hypoplasia of the first metatarsus, absence of the distal phalanx and hypoplasia of the proximal phalanx of the big toe, pelvic dysplasia, bilateral hip dislocation, a constant facial dysmorphism with sparse hair, peculiar ears, severe micrognathism, and retracted and poorly delineated lips. The existence of consanguinity in two of the families, both with two affected siblings, as well as the lack of sex predilection, allow us to postulate that this syndrome is inherited in a recessive manner.**

(*Am J Dis Child* 134:649-653, 1980)

During the past four years, we have studied several patients with an interesting constellation of findings in three unrelated families. The uniqueness of our observations and the similarity of the patients have encouraged us to present our findings as a new hereditary syndrome.

REPORT OF CASES

CASE 1.—A female infant was born after a full-term pregnancy and normal delivery. Weight at birth was 2,650 g and length was 48 cm. This was the first pregnancy of a consanguineous marriage. The father was 25 years old and the mother was 20. Familial investigation did not reveal genetic problems (Fig 1). Both parents were healthy and without physical abnormalities. A recent second pregnancy was spontaneously aborted. Fifteen days after birth, the propositus was found to have a head circumference of 37 cm, sparse scalp hair, and a wide and tense fontanelle. A severe micrognathia was observed and the temporomandibular articulation was anteriorly placed. The lips were markedly retracted and poorly delineated and the nasolabial distance was diminished. Glossoptosis made a pharyngeal examination difficult; dental follicles were present. Posterior and low-set ears were square in shape, with a wide concha, prominent anthelix, and absent lower third of the helix, earlobe, tragus, and antitragus. The eyes appeared small and the intercanthal distance was 25 mm. The nostrils were anteverted (Fig 2). Chest examination revealed a thoracic circumference of 29 cm, and absent clavicles and nipples. A cardiac examination did not reveal any pathologic features. The external genitalia were normal. There was agenesis of the thumb, distal aphalangia, and hypoplastic nails in the other fingers. The second fingers also showed absence of the middle phalanges. Bilateral simian creases were observed. The feet showed agenesis of the great toe and hypoplastic nails. In both hands and feet, the fingers appeared pointed (Fig 3). Both hips were dislocated. The patient died 22 days after birth; an autopsy was not performed. Roentgenologic findings, summarized in Table 1, included a skull with craniofacial disproportion due to hypoplastic facial bones and macrocrania, micrognathia, and glossoptosis. In the vault, especially over the parietal bones and the anterior and posterior fontanelles, the ossification pattern was delayed (Fig 4). The thorax showed bilateral agenesis of the clavicle (Fig 4) and absence of the ossification centers of the sternum. Both hands showed striking alterations, with bilateral absence of all the components of the axial finger and distal aphalangia for the rest of the fingers; the middle phalanx of the second finger was hypoplastic in the right hand and absent in the left (Fig 4). Hypoplastic first metatarsal bones and hypoplastic proximal phalanges of the big toes were found in both feet. Pelvic involvement included flattened acetabuli and less than normal transverse iliac diameter. Bilateral hip dislocation was found.

Patients 2 and 3 were products of the second and third pregnancies from a nonconsanguineous marriage; the father was 30 and the mother was 27 years old. Family history was negative for genetic problems (Fig 1) and both parents were healthy with no physical abnormalities. The first pregnancy produced a boy who developed normally but died of meningitis at 5 months of age.

CASE 2.—This boy was the product of a full-term pregnancy and normal delivery. He lived only one day, and no postmortem examination was done. His physical appearance was remarkably similar to that of

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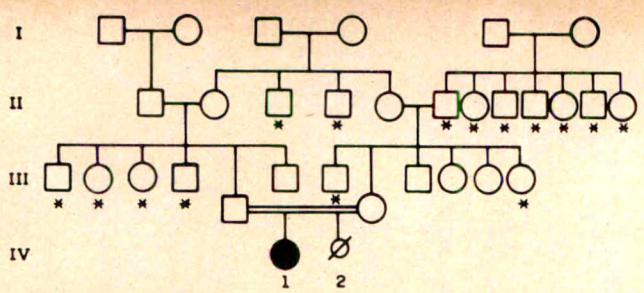
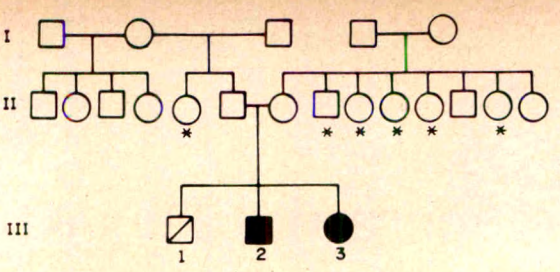


Family 1



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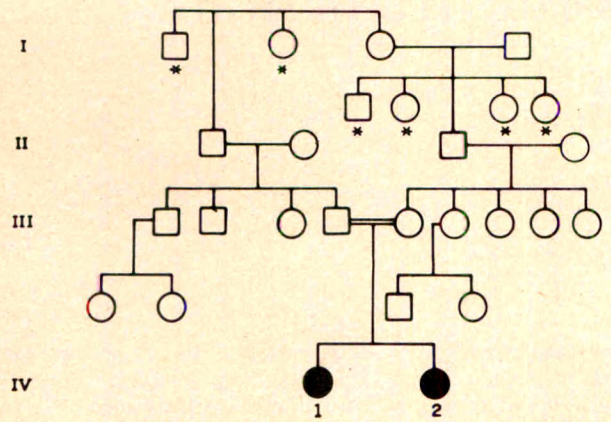

Family 3

* Normal descendants

Fig 1.—Pedigree of three studied families. Consanguinity exists in families 1 and 3. Genetic abnormalities could not be recorded in three or four generations.

Fig 2.—Case 1. Frontal (top left) and lateral (top right) views. Case 3. Frontal (bottom left) and lateral (bottom center) views. Case 4. Lateral view (bottom right). Craniofacial characteristics are clearly visible: craniofacial disproportion, sparse hair, peculiar ears with wide concha, absent tragus, antitragus, and earlobe, poorly defined lips, and severe micrognathia.

Birth weight was 2,500 g, length was [illegible] m, head circumference was 34 cm, and intercanthal distance was 25 mm. His cry was weak. The skull showed sparse hair and a wide fontanelle. Severe micrognathism and anterior temporomandibular articulation were observed. The nasolabial distance was diminished. Posterior and low-set ears showed a prominent anthelix with absence of the lower third of the helix, earlobe, tragus, and antitragus. The nose showed anteverted nostrils. Chest examination revealed a thoracic circumference of 30 cm and absent clavicles. Cardiac examination findings were normal. External genitalia had a male appearance with ectopic testes and micropenis. Bilateral hip dislocation was found. Hands and feet showed the same abnormalities as seen in patient 1, with bilateral thumb agenesis and distal aphalangia in all the fingers. Bilateral simian creases were present. The feet showed agenesis of the big toes. In both hands and feet the digits appeared pointed, with hypoplastic nails. No roentgenologic examination and no laboratory investigations were done in this case.

Case 3.—This female infant was the product of a full-term pregnancy. Her birth weight was 2,300 g, length was 45 cm, head circumference was 34 cm, and intercanthal distance was 24 mm. Clinical examination showed sparse hair, wide fontanelle, diastasis of sutures, depressed temples, and craniofacial disproportion. The facial bones were hypoplastic and a severe micrognathism was observed. The eyes appeared small. The ears, posterior and low set, were remarkably anomalous, with a prominent anthelix and absence of the lower portion of the helix, tragus, antitragus, and earlobe. The nasolabial distance was reduced and a marked labiogingival retraction was present (Fig 2). Chest examination revealed a thoracic circumference of 28 cm and agenesis of both clavicles. Cardiac examination findings were normal. Malformations observed in hands, feet, and pelvis were essentially the same as those observed in cases 1 and 2, including bilateral thumb agenesis, distal aphalangia of the other fingers, bilateral absence of the big toes, and hypoplastic nails in all the fingers (Fig 3, center).

Roentgenologic findings, summarized in Table 1, showed a skull with altered ossification pattern, especially over the parietal bones and the anterior fontanelle; craniofacial disproportion; and hypoplastic facial bones and micrognathia (Fig 4, center left The thorax showed agenesis of the right clavicle and a hypoplastic left clavicle (Fig 4, center right); ossification centers of the sternum were not visible. Both hands had abnormalities, with bilateral absence of all the components of the axial finger and distal aphalangia of the rest of the fingers; the second fingers showed bilateral agenesis of the middle phalanges (Fig 4, bottom left). Hypoplastic first metatarsal bones and hypoplastic proximal phalanges of both big toes were found (Fig 4, bottom right). Pelvic alterations included flattened acetabuli and a small transverse iliac diameter. Bilateral hip dislocation was observed.

Fig 3.—Top, Case 1, view of hands (left) and feet (right). Center, Case 3, view of hands (left) and feet (right). Bottom, Case 4, view of hands (left) and feet (right). Hands and feet, almost identical in all cases, show thumb and big toe agenesis. Hypoplasia of last phalanges and nails as well as pointed appearance of rest of fingers are evident.

Laboratory data for cases 1 and 3 showed normal karyotypes and normal values for the hematologic tests, serum electrolytes, calcium, phosphorus, alkaline phosphatase, urinary calcium, amino acid excretion, and mucopolysaccharide determinations. Autopsy findings were negative, without gross malformations or histologic alterations, with one exception; the brain showed fissures deeper than usual, without alterations of its histologic features.

Patients 4 and 5, both female, were not examined by us. Patient 4 lived 65 days; patient 5, 35 days. The parents' descriptions corresponded to the clinical picture of the other cases, including all the characteristics described in skull, facies, hands, and feet. Birth weight and length were 2,100 g and 43 cm, respectively, for case 4, and 2,300 g and 45 cm for case 5. Both pregnancies were threatened by abortion. The father and mother, aged 27 and 23 years, respectively, are second cousins. No genetic abnormalities were recorded in their families and no physical alterations were present in them (Fig 1). Medical examination of patient 4 revealed a large anterior fontanelle continuous with the posterior fontanelle. An ossification defect of the occipital bone was present. The eyes showed a moderate exophthalmos and hypertelorism. The ears were described as low set and dysplastic. The palate was narrow and arched and a severe micrognathia was seen (Fig 2, bottom). Both hands showed thumb agenesis; absence of the last phalanges and nails was reported for the rest of the fingers. Both feet showed agenesis of the big toe (Fig 3, bottom). Bilateral absence of the clavicle was found. During the clinical

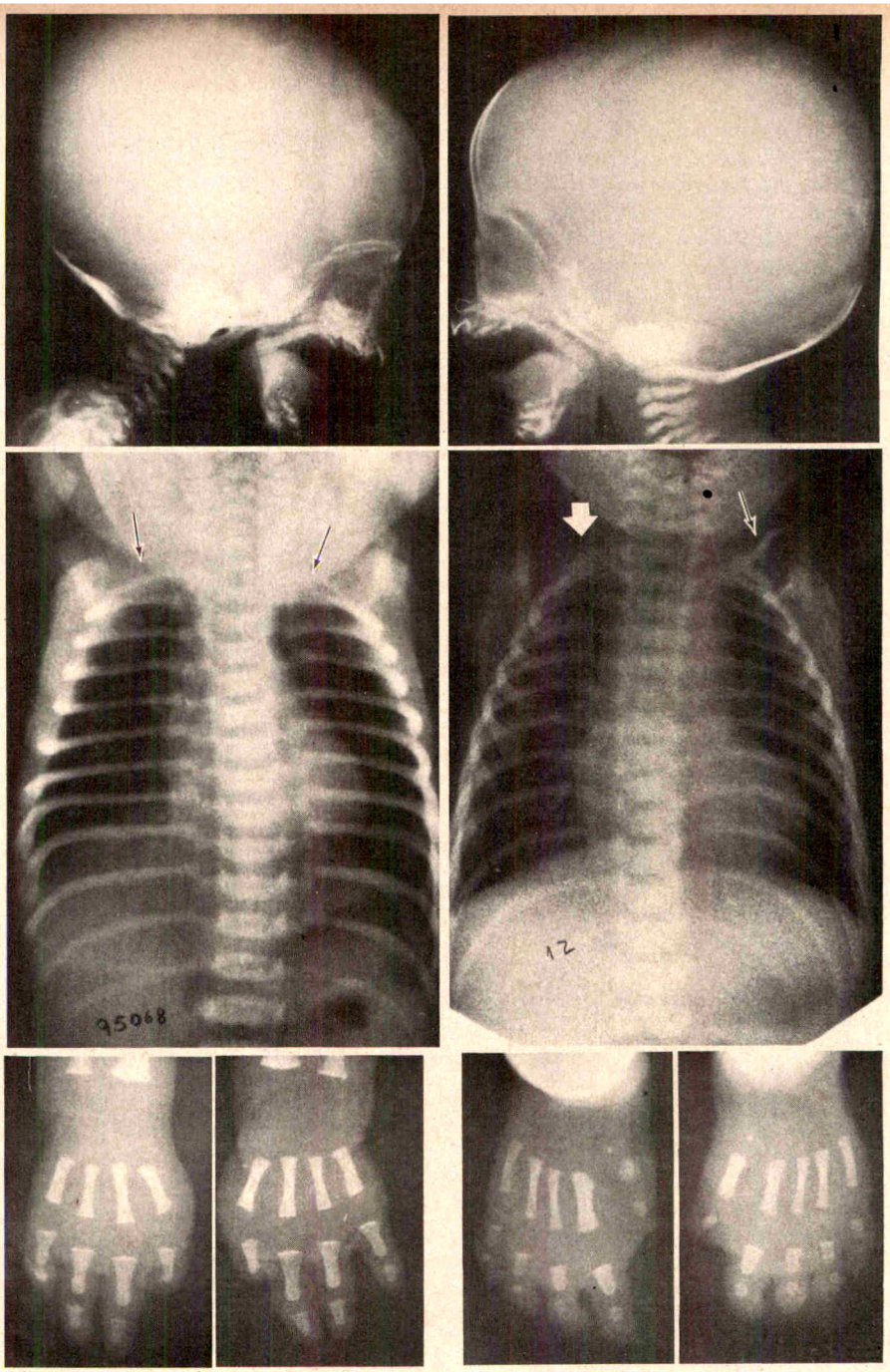

Fig 4.—Roentgenograms showing skull with craniofacial disproportion, hypoplastic facial bones, and micrognathia in patient 1. Note macrocrania and altered ossification pattern with diastasis of the sutures (top left); arrows (center left) show bilateral absence of clavicles, and hands show absence of all components of first fingers and distal aphalangia in rest of them (bottom left). Note that middle phalanx of second finger is hypoplastic in right and absent in left hand. Small differences in relation to (top right, center right, bottom center, and bottom right) are seen in clavicles, where asymetric absence is seen, and hands show bilateral absence of middle phalanges in second fingers. Bottom right, both feet show hypoplastic proximal phalanges in big toes and hypoplastic first metatarsal bone, more severe in right foot.

course, the patient had frequent episodes of respiratory obstruction with cyanosis, requiring intubation until her death. Roentgenologic studies were not done in this case. Autopsy findings included a small thyroid gland, larynx, trachea, lungs, and thymus; the heart was of normal weight and had normal morphologic features. The digestive tract, liver, pancreas, and kidneys were reported to be normal. The brain weighed 300 g, and was normal in shape, but the consistency was harder than usual, with fissures deeper than normal, especially over the frontal lobes. Its histologic features were normal.

Patient 5 was poorly described by the physicians, but the parents said that her physical appearance was similar to that of her sister. Roentgenologic examinations were performed in this case; the results are given in Table 1. Autopsy was not done.

COMMENT

The five patients described herein showed an almost identical clinical and roentgenologic picture. To our knowledge, they represent a syndrome that has not been previously reported. Therefore, we present it as a new hereditary syndrome, the clinical and radiologic characteristics of which are given in Tables 1 and 2.

Although two of the families live in the same general area of the Colombian Andes, in the interior of the country, no known genealogical linkage exists between them. The third family comes from the nothern coast of Colombia, where they have been established for several generations.

The syndrome is present in both sexes, and in two of the families two siblings have been affected; the par-

Table 1.—X-ray Film Findings

Findings	Case 1	Case 3	Case 5
Skull dysostosis	+	+	+
Asymmetry of the skull	+	–	–
Wide fontanelles and separated sutures	+	+	+
Craniofacial disproportion	+	+	+
Macrocrania	+	+	+
Hypoplastic facial bones	+	+	+
Micrognathia	+	+	+
Right clavicle agenesis	+	+	+
Hypoplasia or agenesis of the left clavicle	+	+	+
Absence of the ossification center of the sternum	+	+	+
Dysplastic pelvis with flattened acetabuli and decreased iliac diameter	+	+	NA*
Hip dislocation	+	+	NA
Thumb agenesis	+	+	+
Olygosyndactyly and distal aphalangia of 2nd, 3rd, 4th, and 5th fingers	+	+	+
Agenesis of the mild phalanx of the second right finger	+	+	+
Agenesis or hypoplasia of the mid phalanx of the second left finger	+	+	+
Bilateral hypoplasia of the first metatarsal bone	+	+	+
Bilateral hypoplasia of the proximal and agenesis of the distal phalanges of the big toe	+	+	+

*NA indicates that no x-ray films were available.

Table 2.—Clinical Findings

Features	Case 1	Case 2	Case 3	Case 4*	Case 5†
Age, day	22	1	50	65	35
Sex	F	M	F	F	F
Weight at birth, g	2,650	2,500	2,300	2,100	2,300
Length at birth, cm	48	47	45	43	45
Head circumference, cm	37.0	34.0	34.5	...	...
Skull	Dolicho-cephalus	Dolicho-cephalus	Dolicho-cephalus	Dolicho-cephalus	...
Wide fontanelles and diastasis of sutures	+	+	+	+	+
Hair	Sparse	Sparse	Sparse	Sparse	Sparse
Depressed temples	+	...	+	...	...
Microphthalmia	+	...	+	...	...
Hypoplastic facial bones	+	+	+	+	...
Anteverted nostrils	+	+	+	+	+
Diminished nasolabial distance	+	+	+	+	+
Poorly defined lips	+	+	+	+	+
Micrognathism	+	+	+	+	+
Cystic dental follicles	+	...	+	...	...
Absent nipples	+	–	–	–	...
Narrow and arched palate	+	+	+	+	...
Low-set and mal-formed ears	+	+	+	+	+
Agenesis of clavicles	+	+	+	+	+
Ortolani sign	+	...	+	...	...
Thumb agenesis	+	+	+	+	+
Distal aphalangia in fingers 2, 3, 4, and 5	+	+	+	+	+
Bilateral hypoplasia of first metatarsal bone	+	+	+	+	+
Bilateral hypoplasia of the phalanges of the big toes	+	+	+	+	+

*Case 4 was reconstructed after familial version, medical records, and necropsy findings.
†Case 5 was reconstructed after familial version and after studying x-ray films and photographs.
Ellipses indicate information not available.

ents were healthy in all cases, and no abnormal history, either skeletal or metabolic, could be found in their families. Chromosome abnormality was not found in the patients. Two of the families were consanguineous. These considerations allow us to postulate an autosomal recessive inheritance of this syndrome.

Some of the features presented by our patients, mainly the association of micrognathia and glossoptosis, evident in case 1, are components of the Robin anomaly. However, glossoptosis was not a constant finding, and membranous cleft palate was not found in any of the patients. It may be considered that the clinical picture of our patients is somewhat similar to cleidocranial dysplasia, and this is the reason for making some comparisons between these two entities. Cleidocranial dysplasia shows a deficiency in the ossification of the skull with a delay in the closure of the anterior fontanelle, which gives a specific shape to the skull and the forehead. In addition, the hypoplastic maxilla makes for an apparent craniofacial disproportion. The ossification of the clavicles is altered, frequently asymetrically.[1] The features we have mentioned are common to both syndromes, but the differences are remarkable in other aspects: pelvic involvement with delayed ossification of the pubic bone and hypoplasia of the iliac wings are present in cleidocranial dysplasia and they are not in this syndrome. Hand anomalies in cleidocranial dysplasia, which include brachymesophalangia and a characteristic pointing of the terminal tufts of the phalanges with hypoplastic changes evident in the thumbs,[1] are not closely similar to the thumb and first metacarpal agenesis and distal aphalangia that was constant in our five patients. Moreover, the severe micrognathism, peculiar facial dysmorphism, the changes related to the feet, and the recessive genetic pattern are good reasons to differentiate these two entities. Finally, the limited laboratory determinations that we have performed have revealed no biochemical alterations in any of the patients.

Reference

1. Jarvis JL, Keats TE: Cleidocranial dysostosis: A review of 40 new cases. *Am J Roentgenol* 121:5-16, 1974.

Juvenile Chronic Granulocytic Leukemia

Emphasis on Cutaneous Manifestations and Underlying Neurofibromatosis

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• Five patients with juvenile chronic granulocytic leukemia are described. Two patients had multiple cafe-au-lait spots compatible with von Recklinghausen's neurofibromatosis, and three had cutaneous xanthomata. Recurrent cutaneous leukemic infiltrates were noted in two patients. The clinical course of all five patients was characterized by recurrent respiratory symptoms and pulmonary infiltrates that responded to antileukemic therapy in three. Chemotherapy controlled the symptoms but did not influence the eventually fatal outcome.

(*Am J Dis Child* 134:654-658, 1980)

The classification of chronic granulocytic leukemia (CGL) in children has been subdivided into juvenile or adult type based on clinical, hematologic, and cytogenetic data.[1-4] The usual criteria for the juvenile type include early age at onset, absence of the Philadelphia chromosome, presence of fetal RBC characteristics, early onset of severe thrombocytopenia, and rapid death in spite of therapy. The adult form tends to occur in older children, is associated with the Philadelphia chromosome, lacks fetal cell characteristics, runs a more chronic course, and responds to therapy with alkylating agents. A recent proposal, based on growth characteristics of peripheral blood cells in culture suggests that the juvenile type of CGL is actually a monocyte-predominant panmyelopathy whereas the adult type is a true granulocytic leukemia.[5-6]

We report five cases of characteristic juvenile type CGL. Two of these five unrelated cases were found to have von Recklinghausen's neurofibromatosis. Three of the five had associated cutaneous xanthomata. The association of juvenile CGL with neurofibromatosis and cutaneous xanthomata is reviewed.

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Reprints not available.

MATERIALS AND METHODS

Hematologic studies, ie, erythrocyte I,i surface antigen determination, and leukocyte alkaline phosphatase, were performed by standard techniques. Fetal hemoglobin value was estimated by the alkaline denaturation method of Singer, and the intracellular distribution of fetal hemoglobin by a modification of the Betke stain.[7,8] Hemoglobin A_2 was quantitated after cellulose acetate electrophoresis[9] and was confirmed by microchromatography on diethylaminoethyl cellulose-52 (DE-52).[10] Red cell carbonic anhydrase B was quantitated by cellulose acetate electrophoresis and by Mancini et al immunodiffusion.[11] The glycine-alanine composition of peptide γ-CG3 was determined by described methods.[12] Cytogenetic studies were by standard methods. Bone marrow specimens were aspirated, and an aliquot was suspended in demecolcine (Colcemid) for two hours before direct preparations were made. Banding was performed by Giemsa and quinicrine mustard techniques.[13,14] Fibroblast karyotypes were prepared by standard methods.[15] Agar bone marrow cultures were performed by the method of Pike and Robinson.[16] The colony stimulating activity (CSA) was determined by described methods.[17]

REPORT OF CASES

The laboratory and clinical observations of the five cases are summarized in Tables 1 and 2.

Case 1.—This male infant was the full-term product of an unremarkable pregnancy and delivery. The newborn period was complicated by group B streptococcus septicemia that responded to antibiotics, phototherapy, and exchange transfusion.

At age 2 months, the patient's WBC count was 30,000/cu mm, with an occasional blast cell seen. The gradual onset of splenic and hepatic enlargement led to hematologic investigation at age 6 months (Table 1). A bone marrow aspirate indicated severe myeloid hyperplasia, but no Philadelphia chromosome was found on direct karyotype preparation. In vitro bone marrow cultures revealed preponderant monocytic differentiation. The serum CSA was greatly elevated. Splenectomy was performed, and extramedullary hematopoiesis was demonstrated in the spleen, mesenteric lymph nodes, and liver. The leukocytosis and thrombocytopenia were unaffected by splenectomy.

The patient had chronic tachypnea and variable interstitial pulmonary infiltrates. At 8 months of age, he had a massive pericardial effusion develop that was relieved by pericardiocentesis. The fluid was sterile and contained no malignant cells. A four-week trial with busulfan therapy resulted in no change in the hematologic values. Prophylactic penicillin G potassium and folic acid were given during the ensuing 19 months. The patient's liver and peripheral lymph nodes enlarged moderately, and chronic respiratory distress continued. The WBC counts remained at about 150,000/cu mm, hemoglobin level, 10 g/dL; and platelet counts, 40,000 to 60,000/cu mm. At age 27 months, he died in bed a few hours after the onset of mild upper respiratory tract symptoms.

Acute pneumonia associated with desquamation of bronchial mucosa was found at autopsy. Marked numbers of atypical inflammatory cells were noted to cuff the peripheral airways. Leukemic infiltrates were noted in all organ systems.

Case 2.—A 2-year-old boy had *Salmonella* enteritis. The patient and his father were known to have neurofibromatosis. Examination showed a chronically ill infant with developmental delay. The liver was palpable 3 cm below the right costal margin and the spleen was palpable 4 cm below the left costal margin. The skin showed multiple facial and scalp xanthomata, multiple truncal cafe-au-lait lesions, and scattered eczematoid lesions on the anterior abdominal wall. Moderate enlargement of the inguinal and submandibular nodes was noted. Results of studies performed at the time of this hospital admission are given in Table 1. Bone marrow aspiration indicated granulocytic hyperplasia with rare megakaryocytes. Marrow karyotype showed 46,XY,Y inversion. The inversion was also present in the patient's skin fibroblast karyotype,

Table 1.—Laboratory Data at First Visit*

	Case				
	1	2	3	4	5
Age	6 mo	23 mo	4 yr 8 mo	7½ yr	2½ yr
Sex	M	M	M	M	M
Chemical and formed elements of blood					
Hemoglobin, g/dL	7.1	12.2	10.1	11.9	12.3
Platelets/cu mm	25,000	90,000	19,000	12,000	64,000
WBCs/cu mm	100,000	89,000	159,000	30,600	58,000
Differential cell count, %					
Polymorphonuclear leukocytes	45	47	70	47	30
Lymphocytes	11	26	12	18	29
Monocytes	14	20	5	10	8
Myelocytes	13	. . .	5	10	2
Metamyelocytes	10	2	2	10	. . .
Promyelocytes	4	2	5	. . .	. . .
Blasts	2	. . .	. . .	5	3
Nucleated RBCs	10	2	2	6	1
RBC dysmorphology	+	+	+	+	+
Leukocyte alkaline phosphatase	?	N	N	N	N
Serum vitamin B_{12}, pg/mL (normal, 300-1,000)	> 1,600	> 1,600	> 1,600	> 1,600	> 1,600
Marrow karyotype	46,XY	46,XY Inv Y	46,XY	46,XY	46,XY
Serum lysozyme, μg/mL (normal, 2.8-8.0)	7.8	6.5	5.5	ND	22
Fetal hemoglobin, %					
Betke-Kleihauer method[6] (normal < 1%)	50	52	94	86	75
Singer et al method[7] (normal < 2%)	18.8	37.3	57	42.3	50.1
Carbonic anhydrase B	Decreased	Decreased	Decreased	Decreased	Absent
Erythrocyte I,i surface antigen ratio (normal > 10:1)	ND	1:1	"Inverse"	1:1	1:1
Hemoglobin A_2, % (normal 1.9-3.2)	2.1	0.8	1.1	0.8	0.7

*Plus sign indicates present; N, normal value; Inv Y, Y inversion; ND, not determined.

but it was not present in the peripheral blood karyotype of the patient's father. No Philadelphia chromosome was identified. In vitro bone marrow cultures disclosed differentiation that was preponderantly monocytic macrophages. Serum CSA was extremely elevated.

Chemotherapy was deferred because of pertussis-like illness characterized by paroxysms of coughing and by diffuse perihilar interstitial pulmonary infiltrates. The patient had a right flaccid hemiplegia develop during a 24-hour period in conjunction with a WBC count of 116,000/cu mm and a platelet count of 12,000/cu mm. Computerized axial tomography (CT) showed focal edema in the internal capsule, suggestive of hemorrhage.

Treatment was begun with platelet transfusions and combination chemotherapy (prednisone, thioguanine, doxorubicin hydrochloride [Adriamycin], cytarabine [cytosine arabinoside] hydrochloride and vincristine sulfate). After two seven-day courses of therapy, the bone marrow contained abundant megakaryocytes and there was reduction in granulocytic hyperplasia. Spleen size sharply decreased. The peripheral WBC count was now 15,000/cu mm (with occasional blast form), hemoglobin level was 9.7 g/dL, and platelet count was 267,000/cu mm. The patient received an additional five-day course of chemotherapy. Cranial irradiation (2,400 rads) and intrathecal methotrexate sodium (12 mg/sq m on five occasions) were given during a three-week period when the CSF was noted to contain blast cells.

The patient remained relatively well for three months with WBC counts less than 30,000/cu mm. His activity then decreased coincident with severe splenic enlargement. Indurated and erythematous skin lesions were noted on the abdominal wall. These lesions had an elevated circular border with central sparing and measured 4 to 6 cm in diameter. Biopsy specimen showed leukemic infiltrates. The cutaneous infiltrates resolved spontaneously during the next six weeks as the WBC count increased to 80,200/cu mm and the platelet count decreased to 39,000/cu mm.

Treatment with combination chemotherapy was again instituted, and dramatic reduction in spleen size was accompanied by decrease in WBC count and elevation in platelet count. Chemotherapy was administered on an intermittent basis as dictated by the WBC count, splenomegaly, and pulmonary symptoms. A similar but less dramatic response to therapy with azacitidine was noted. His condition remained one of slow deterioration and he died 18 months after diagnosis. No autopsy was performed.

Case 3.—A 4-year 8-month-old boy had an acute respiratory illness. Examination showed a chronically ill appearing boy with protuberant abdomen and scattered petechiae. The liver was enlarged 4 cm below the right costal margin, and a firm spleen was palpable to the iliac crest. Moderate

Table 2.—Clinical Data and Course for Patients With Juvenile CGL*

	Case				
	1	2	3	4	5
Splenomegaly	+	+	+	+	+
Hepatomegaly	+	0	+	0	+
Leukemic skin infiltrate	0	+	0	0	+
Xanthoma	0	+	0	+	+
Cafe-au-lait spots	0	+	0	+	0
Eczema	0	+	0	0	0
Pulmonary infiltrates	+	+	+	+	+
Treatment					
Splenectomy	+	0	0	0	0
Splenic radiation	0	0	+	0	+
Cranial radiation	0	+	0	0	0
Chemotherapy	0	+	+	0	+
Survival from diagnosis, mo	21	18	5	5	14

*CGL indicates chronic granulocytic leukemia; plus sign, present or performed; zero, absent or not performed.

peripheral node enlargement was present. No cafe-au-lait lesions or xanthomata were seen. Results of laboratory studies are given in Table 1. Alpha-chain analysis of the fetal hemoglobin disclosed a glycyl residue at position 136 (G_γ). Bone marrow aspirate was hypercellular, with granulocytic hyperplasia, rare megakaryocytes, and a 46,XY karyotype with no Philadelphia chromosome. Family history was unknown (adopted). Treatment was begun with combination chemotherapy as in case 2, with resultant decrease in marrow cellularity, reduction in peripheral WBCs to 17,000/cu mm, and platelet elevation to 82,000/cu mm. The splenic size decreased greatly within 72 hours of chemotherapy. Chemotherapy was repeated at monthly intervals on three occasions, with resultant temporary response in all variables. His clinical course was complicated by recurrent pulmonary dysfunction resembling acute bronchospasm with shifting atelectasis. This was poorly responsive to antibiotics and bronchodilators but responded to cytoreductive chemotherapy. Five months from initial examination, he had painful enlargement of the spleen coincident with a blast crisis and leukocytosis of 500,000/cu mm. His condition was refractory to treatment with platelet transfusions, splenic radiation, and chemotherapy, and he died from intracranial bleeding.

Autopsy findings indicated leukemic infiltrates about many of the bronchi. Within the pulmonary parenchyma, focal necrosis was noted but no organisms were seen. Pleural fluid and pleural adhesions were noted on the right. Leukemic infiltrates were demonstrated in most organ systems.

Case 4.—A 7½-year-old boy was vomiting and had diarrhea and fever. Examination showed an undergrown, chronically ill-appearing boy with multiple cafe-au-lait spots over the trunk and axillae, bilateral papilledema, and severe splenomegaly. A xanthoma was noted on the left knee. Laboratory data on admission are given in Table 1. Bone marrow aspirate was hypercellular, with a myeloid-erythroid ratio of 10:1. Megakaryocytes were decreased in number. Bone marrow karyotype revealed 46,XY with no Philadelphia chromosome. In vitro marrow culture disclosed preponderantly monocytoid differentiation. Serum CSA was slightly increased. Family history was unknown (adopted). Limited investigations were allowed, and all therapy was refused by the foster parents. The CT and roentgenograms of the optic foramina and skull showed no abnormalities. The CSF contained normal amounts of protein and glucose and no cells. The patient was readmitted to the hospital in acute respiratory distress one month later, at which time he had right lower lobe collapse. He continued to suffer coughing paroxysms during a two-month period prior to his death, and he finally became blind and hemiparetic before his death. No autopsy was performed.

Case 5.—A 2½-year 1-month-old boy was noted at routine examination to have splenomegaly and leukocytosis. Examination showed a spleen palpable 7 cm below the left costal margin, liver 4 cm below right costal margin, and mild cervical adenopathy. Numerous maculopapular erythematous lesions were noted over the right thigh and anterior tibia. Biopsy specimen of a skin lesion showed perivascular foci of immature inflammatory cells without xanthomatous or neurofibromatous component. A juvenile xanthogranuloma had been excised from the scalp at 1 year of age. There was no family history of neurofibromatosis, xanthomata, or leukemia. Results of hematologic studies are given in Table 1. Bone marrow aspirate was hypercellular, with decreased megakaryocytes and increased myeloid/erythroid ratio. The bone marrow karyotype was normal, 46,XY, and no Philadelphia chromosome was identified. In vitro bone marrow culture disclosed spontaneous colony formation with preponderantly monocyte maturation. Serum CSA was greatly elevated.

The patient received no treatment for six months after initial visit. Gradual deterioration with increasing leukocytosis and progressive hepatosplenomegaly subsequently led to three courses of combination chemotherapy resulting in decreased WBC count and decreased splenomegaly. His course was characterized by recurrent hepatosplenomegaly, leukemic infiltrates of the abdominal and chest wall, and recurrent pulmonary symptoms. A liver-spleen scan showed persistent splenic hypofunction unchanged by chemotherapy or splenic irradiation. He died 14 months after diagnosis. Autopsy was not performed.

COMMENT

The majority of children with the myeloproliferative disorder called CGL can be classified into the juvenile or adult type.[2] Familial forms of the disease as well as occasional patients who defy classification may also be seen.[2] The disease is characterized by peripheral leukocytosis with increased numbers of granulocytic cells at all levels of maturation. Results of bone marrow examination are abnormal in that there is a relative and absolute increase in granulocytic cells at all levels of maturation without a preponderance of blast forms. Megakaryocytes are decreased in the juvenile form but present in normal numbers in the adult form. Monocytosis is frequently noted in juvenile CGL, and in vitro cell cultures produce preponderantly monocytic colonies.[6,17] Because of this observation, it is postulated that juvenile CGL is a form of acute monocytic leukemia.[5] The elaboration of CSA by a malignant monocyte may be responsible for the associated neutrophilia. The persistent CSA production in the presence of neutrophilia suggests a defect in feedback inhibition.[17]

Chronic granulocytic leukemia of either variety is rare in childhood. In a recent review of 649 cases of childhood leukemia at St Jude's Children's

Research Hospital, Memphis, Tenn, only 18 patients (2.8%) were found to have CGL and six of these were classified as having the juvenile form.[2] Weisgerber et al reported an experience of 25 cases of juvenile CGL during a 14-year period in France.[18] Eisenberg and Wallerstein found 30 cases in the literature prior to 1934 and Hardisty et al an additional 104 cases prior to 1964.[1,19] Approximately 50 additional cases can be found in the literature.[20-32]

Juvenile CGL is a disease seen primarily in male subjects. In a recent series of 12 well-studied cases, 11 were male.[33] Our five patients with juvenile CGL were all male. In the same time period, three other patients with the clinical picture of CGL were seen. One male patient had the adult form with the Philadelphia chromosome while two female patients (one with associated neurofibromatosis) were not classifiable into either the adult or juvenile form. No sex-linked pattern of inheritance has been noted.

Previous reports have stressed an eczematoid facial rash as part of the clinical picture in juvenile CGL.[1,34] Only one of our patients had an eczematoid rash. It was located on the trunk and was not clinically important. Two patients showed recurrent leukemic skin infiltrates that were varied in their appearance. Case 5 showed erythematous maculopapular lesions scattered over the legs while case 2 showed the curious circular areas of induration and erythema with central clearing. These lesions appeared frequently and did not appear to be related to chemotherapy. In none of our cases did a previously recognized leukemic infiltrate become xanthomatous, as has been suggested in a case of adult CGL.[35]

The most consistent skin lesions were xanthomata, which were noted in three of the five patients (Table 2). In two cases, the onset of xanthomata antedated the leukemia diagnosis by one year, and in one case, it was noted at the time of the leukemia diagnosis. Conditions previously associated with xanthomata in children include histiocytosis, familial hyperlipidemia, hypothyroidism, and the glycogenoses.[36] Xanthomata have been reported to precede and accompany leukemia in children and adults. Thelander in 1949 described an infant who (1) at 3 months of age was noted to have scalp xanthomata, (2) at 6 months had a diagnosis of myelogenous leukemia with massive hepatosplenomegaly, and (3) at 26 months died after intermittent respiratory insufficiency.[37] Denys and Malbrain[38] proposed the term "xantholeukemia" when reporting a similar case, noting two similar cases reported by Crocker.[39] Eleven similar cases of childhood myelogenous leukemia and xanthomata have been reported.[1,40-43]

Two of the five patients had multiple cafe-au-lait spots compatible with the diagnosis of neurofibromatosis, and both of these also had cutaneous xanthomata. An association between xanthoma and neurofibromatosis has been well documented.[44-46] Since xanthoma may be the earliest manifestation of neurofibromatosis, one could postulate that case 5 may have had underlying neurofibromatosis as well.[47]

Royer et al first noted the coincidence of neurofibromatosis and childhood leukemia.[48] Subsequent reports have emphasized the association between leukemia, neurofibromatosis, and cutaneous xanthomata, so that the interrelationship seems firmly established.[28-31,40,47-51] Of interest is the high incidence of nonlymphocytic leukemia in patients with neurofibromatosis when compared with that noted in a general pediatric population.[47] Of 29 cases of neurofibromatosis and leukemia reviewed by Bader and Miller,[47] 20 had nonlymphocytic leukemia, and eight of these were CGL. The addition to this group of our three cases (two juvenile CGL, one unclassified CGL) would give a total of 32 cases, of which 11 (34%) had the combination of neurofibromatosis and CGL. In view of the relative rarity of CGL in children, the preponderance of CGL noted in association with neurofibromatosis is striking. Also of interest is the rather low incidence of the adult form of CGL (Philadelphia chromosome present) in this group—two out of 11 cases when considering our patients and those reviewed by Bader and Miller.[47]

Previous studies have not reported chromosomal abnormalities in patients with combined CGL and neurofibromatosis other than the presence of the Philadelphia chromosome in patients with the adult form.[47] In our patients, chromosome analysis using Giemsa and quinacrine mustard banding techniques revealed no abnormalities other than the 46,XY,Y inversion noted in case 2. The presence of the same alternation in skin fibroblasts of this patient make it unlikely that it was associated with malignant hematopoietic cell lines.

Pulmonary symptoms were a continuing problem in our patients. These symptoms varied from chronic tachypnea and cough to episodes of bronchospasm with expiratory wheezing and emphysema. The latter picture was unchanged by administration of epinephrine hydrochloride (Adrenalin) or bronchodilators. No episodes of bacterial pneumonia were seen, and antibiotic therapy did not alter the clinical course. Although no antemortem lung biopsies were performed, postmortem specimens did not disclose evidence of viral or fungal disease. Roentgenographic studies repeatedly demonstrated shifting atelectasis. Cytoreductive chemotherapy seemed to relieve the pulmonary symptoms and was particularly effective for patients with a bronchospastic component. Autopsy confirmation of peribronchial cuffing by immature granulocytes would support a malignant rather than an infectious etiology for the respiratory symptoms. A direct association between respiratory distress and the blood leukocyte doubling rate has been shown in hyperleukocytic leukemias.[52] Documented infection was negligible in all patients despite frequent chemotherapy-induced neutropenia. Suppurative adenopathy, previously stressed as characteristic of juvenile CGL, was not seen although patient 2 did have an episode of staphylococcal pyoderma.[34]

The best form of therapy for juvenile CGL remains to be determined. The poor response to alkylating agents has been well publicized and was noted in the one patient in whom it was attempted.[34] Because of the proposal that juvenile CGL is a form

of acute monocytic leukemia, attempts have been made to treat juvenile CGL with therapeutic regimens used for acute nonlymphocytic leukemia.[53] Of our three patients treated with combination chemotherapy, all had clinical and cytologic response with minimal toxic effects. The response by patient 3 was short with a five-month survival, whereas patient 2 survived 18 months and patient 5 survived 14 months. The two patients who did not receive intensive chemotherapy survived 21 months and five months. It has been suggested that optimally timed administration of combination chemotherapy may improve the quality of life rather than survival time.[53] Our observation of these five patients tends to support this view.

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Nonproprietary Name and Trademark of Drug

Vincristine sulfate—*Oncovin*.

References

1. Hardisty RM, Speed DE, Till M: Granulocytic leukaemia in childhood. *Br J Haematol* 10:551-566, 1964.

2. Smith KL, Johnson W: Classification of chronic myelocytic leukemia in childhood. *Cancer* 34:670-679, 1974.

3. Bloom GE, Gerald PS, Diamond LK: Chronic myelogenous leukemia in an infant: Serial cytogenetic and fetal hemoglobin studies. *Pediatrics* 38:295-299, 1966.

4. Reisman LE, Trujillo JM: Chronic granulocytic leukemia of childhood: Clinical and cytogenetic studies. *J Pediatr* 62:710-723, 1963.

5. Altman AJ, Baehner RL: In vitro colony-forming characteristics of chronic granulocytic leukemia in childhood. *J Pediatr* 86:221-224, 1975.

6. Altman AJ, Palmer CG, Baehner RL: Juvenile 'chronic granulocytic' leukemia: A panmyelopathy with predominant monocytic involvement and circulating monocyte colony-forming cells. *Blood* 43:341-350, 1974.

7. Singer K, Chernoff AI, Singer L: Studies on abnormal hemoglobins: I. Their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation. *Blood* 6:413-428, 1951.

8. Betke K, Kleihauer E: Fetaler and bleibender Blutfarbstoff in Erythrozyten und Erythroblasten von menschlichen Feten and Neugeboren. *Blut* 4:241-249, 1958.

9. Ruiz-Reyes G, Ramirez-Zorilla MJ: Rapid measurement of erythrocyte carbonic anhydrase isozymes by means of cellulose acetate membrane electrophoresis. *Am J Clin Pathol* 50:677-682, 1968.

10. Efremov CD, Huisman THJ, Bowman K, et al: A rapid method for the determination of hemoglobin A_2. *J Lab Clin Med* 83:657-664, 1974.

11. Mancini O, Carbonara AO, Heremans JF: Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 2:235-254, 1965.

12. Schroeder WA, Huisman THJ, Shelton JR, et al: Evidence for multiple structural genes for the gamma chain of human fetal hemoglobin. *Proc Natl Acad Sci USA* 60:537-544, 1968.

13. Arrighi FE, Hsu TC: Localization of heterochromatin in human chromosomes. *Cytogenet* 10:81-86, 1971.

14. Caspersson T, Lomakka G, Zech L: The 24 fluorescence patterns of the human metaphase chromosomes: Distinguishing characters and variability. *Hereditas* 67:89-102, 1971.

15. Harnden DG: A human skin culture technique used for cytological examinations. *Br J Exper Pathol* 41:31-37, 1960.

16. Pike BL, Robinson WA: Human bone marrow colony growth in agar gel. *J Cell Physiol* 76:77-84, 1970.

17. Bagby GC, Bailey S, Neerhout RC: Defective feedback regulation of granulopoiesis in juvenile granulocytic leukemia (JCGL). *Exp Hematol* 5:60, 1977.

18. Weisgerber C, Schaison G, Seligmann M, et al: Les leucemies myelomonocytaires du petit enfant. *Bull Cancer* 56:351-364, 1969.

19. Eisenberg AA, Wallerstein H: Chronic myelosis in children. *J Lab Clin Med* 19:713-723, 1934.

20. Pochedly C: Unusual manifestations of chronic granulocytic leukemia in a child. *Cancer* 24:1017-1020, 1969.

21. Talvalkar GV: Chronic myeloid leukemia in children. *J Assoc Physicians India* 13:47-50, 1956.

22. Chatterjea JB, Ghose S, Ray RN: Incidence of leukemia: An analysis of 544 cases studied in Calcutta. *J Assoc Physicians India* 10:673-676, 1962.

23. Ritz ND, Purfar M: Chronic myeloid leukemia with priapism in 8-year-old child. *NY State J Med* 64:553-556, 1964.

24. Iversen T: Leukaemia in infancy and childhood: A material of 570 Danish cases. *Acta Paediatr Scand* 167(Suppl):173-176, 1966.

25. Vasavada PS, Ali A, Mukerji DP: Clinical studies in leukemia: Review of 100 cases. *J Assoc Physicians India* 10:677-682, 1962.

26. Ramakumar L, Prakash C, Sood SC, et al: Chronic myeloid leukaemia in childhood. *Indian J Pediatr* 30:81-86, 1963.

27. Fox AM: Case of juvenile chronic myeloid leukemia. *Lancet* 1:368-369, 1970.

28. McEvoy MW, Mann JR: Neurofibromatosis with leukemia. *Br Med J* 3:641, 1971.

29. McWhirter WR, Savage DCL, Williams BM: Neurofibromatosis with leukemia. *Br Med J* 4:114-115, 1971.

30. Fraumeni JF: Neurofibromatosis and childhood leukemia. *Br Med J* 4:489-490, 1971.

31. Cockington RA: Leukaemic infiltration of the gastrointestinal tract: An unusual cause of protein-losing enteropathy. *Med J Aust* 1:103-105, 1975.

32. Germain D, Trouillas P, Robert JM: Leucemies de l'enfant et maladie de Recklinghausen (a propos de five observations dont two leucemies familiales). *Nouv Rev Fr Hematol* 12:555-560, 1972.

33. Sheridan BL, Weatherall DJ, Clegg JB, et al: The patterns of fetal haemoglobin in leukaemia. *Br J Haematol* 32:487-506, 1976.

34. Mauer AM, Lampkin BC, McWilliams NB: The leukemias and reticuloendotheliosis, in Nathan DG, Oski FA (eds): *Hematology of Infancy and Childhood*. Philadelphia, WB Saunders Co, 1974, vol 22, pp 665-730.

35. Lynch PJ, Winkelmann RK: Generalized plane xanthoma and systemic disease. *Arch Dermatol* 93:639-646, 1966.

36. Crocker AC: Skin xanthomas, in Vaughan VC, McKay J, Nelson WE (eds): *Nelson Textbook of Pediatrics*, ed 10. Philadelphia, WB Saunders Co, 1975, pp 462-464.

37. Thelander HE: Xanthomatosis. *J Pediatr* 34:490-496, 1949.

38. Dénys P, Malbrain H: Contribution a l'etude des reticuloendothelioses de l'enfant (la xantho-leucemie). *Arch Fr Pediatr* 11:707-716, 1954.

39. Crocker AC: Skin xanthomas in childhood. *Pediatrics* 8:573-597, 1951.

40. Benheim M, Moriquand C, Francois R, et al: Reticulose histio-monocytaire du nourrisson a forme de xanthomatose cutanee. *Pediatrie* 11:399-408, 1956.

41. Emery JL, Lorber J, Sheward JD: Mental retardation, pigmentation of the skin, xanthomatosis, and leukaemia. *Arch Dis Child* 30:542-545, 1955.

42. Freud P, Plachta A, Speer FD, et al: Leukemic xanthomatosis. *Am J Dis Child* 88:43-61, 1954.

43. Schaison G, Weisgerber C, Seligmann M, et al: Les leucemies myelomonocytaires avec xanthomes. *Nouv Rev Fr Hematol* 10:284-288, 1970.

44. Jensen NE, Sabharwal S, Walker AE: Naevoxanthoendothelioma and neurofibromatosis. *Br J Dermatol* 85:326-330, 1971.

45. Newell GB, Sonte OJ, Mullins JF: Juvenile xanthogranuloma and neurofibromatosis. *Arch Dermatol* 107:262, 1973.

46. Sourreil MM, Beylot C, Bioulac P: L'association du xanto-granulome juvenille et de la maladie de Recklinghausen. *J Med Lyon* 53:1165-1171, 1972.

47. Bader JL, Miller RW: Neurofibromatosis and childhood leukemia. *J Pediatr* 92:925-929, 1978.

48. Royer P, Bondet C, Guihard J: Xantholeucemi du nourrisson et neurofibromatose de Recklinghausen. *Ann Pediatr* 34:1504-1513, 1958.

49. Larregue M, Belaich S, Delzant O: Xanthomatoleucemie du jeune enfant et maladie de Recklinghausen. *Ann Dermatol Syphiligr* 99:373-380, 1972.

50. Mouriquand C, Jeune M, Charrat A, et al: Reticulose histomonocytaire avec xanthomes cutanes discussion d'une neurofibromatose associee. *Pediatrie* 15:683-686, 1960.

51. Reich SD, Wiernik PH: Von Recklinghausen neurofibromatosis and acute leukemia. *Am J Dis Child* 130:888-889, 1976.

52. Vernant JP, Brun B, Mannoni P, et al: Respiratory distress of hyperleukocytic granulocytic leukemias. *Cancer* 44:264-268, 1979.

53. Lilleyman JS, Harrison JF, Black JA: Treatment of juvenile chronic myeloid leukemia with sequential subcutaneous cytarabine and oral mercaptopurine. *Blood* 49:559-562, 1977.

Pneumococcal Empyema

Outcome of Medical Management

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• Physicians vary considerably in their opinion as to the duration of hospitalization and degree of surgical intervention for children with pneumococcal empyema. The development of pneumatoceles and persistence of fever or loculated pleural fluid are causes of debate and concern. We reviewed the records of 21 children with confirmed pneumococcal pneumonia. Ten of the 12 with no pleural fluid became afebrile within 48 hours of appropriate antibiotic therapy, whereas the nine with empyema remained febrile an average of 7.1 days (minimum estimate) in spite of documented sterile cultures within 24 hours in five of the patients. Although chest tube and thoracentesis drainage could not remove all the pleural fluid, and pneumatoceles developed in five of the nine children, long-term follow-up studies including chest roentgenograms and pulmonary function testing demonstrated a gradual but complete recovery that did not require long-term hospitalization, continued parenteral antibiotic therapy, or invasive surgical procedures.

(*Am J Dis Child* 134:659-662, 1980)

Pneumococcal empyema is a disease that, by many reports,[1-5] has decreased in frequency of occurrence, perhaps due to a concomitant decrease in pneumonia caused by *Streptococcus pneumoniae*. Early outpatient antibiotic therapy may explain this apparent change in incidence; Siegel et al[6] have recently described ten patients with confirmed pneumococcal empyema of whom seven were culture-negative (etiology established by counterimmunoelectrophoresis [CIE]) due to the prior administration of antibiotics. The observation that these patients spent an average of 18 days in the hospital suggests that questions regarding management of empyema caused by *S pneumoniae* may go beyond the selection of appropriate antibiotic therapy. Prolonged fever, incomplete drainage of the pleural space, and development of pneumatoceles may all generate physician anxiety that could result in more vigorous surgical therapy or prolonged hospital observation.

The following is a report of nine cases of proved pneumococcal empyema with a high frequency of pneumatocele formation and prolonged fever despite effective antibacterial therapy. Long-term follow-up on eight of these children in the form of chest roentgenograms and pulmonary function studies in five provides evidence to support a patient, conservative approach to the management of pneumococcal empyema.

SUBJECTS AND METHODS

A retrospective chart review of all children discharged from the Children's Hospital of Denver with the diagnosis of pneumococcal empyema or pneumonia for the years 1971 through 1977 was undertaken. Sixty-two of 77 charts were available. 24 of these were selected for review because of documentation of etiology by positive blood, pleural fluid, or tracheal aspirate cultures. Antibiotic susceptibility testing was not routinely performed on these isolates.

Pulmonary function tests were administered in respiratory therapy and anesthesiology departments. Measurements included forced expiratory volume, forced vital capacity, expiratory reserve volume, functional residual capacity, residual volume, total lung capacity, single-breath nitrogen washout, and flow-volume loop.

Initial and follow-up chest roentgenograms of all children with pleural fluid were reviewed by a pediatric radiologist.

RESULTS

Of the 62 patients reviewed, 23 had confirmed *S pneumoniae* pneumonia by pleural fluid, blood, or tracheal aspirate culture. One additional patient, who had received previous antibiotic therapy, had the diagnosis confirmed by CIE of pleural fluid. Tracheal aspirates were performed under direct visualization of the larynx in patients with febrile lobar pneumonia. A predominant growth of *S pneumoniae* associated with neutrophils on Gram's stain was considered presumptive evidence of pneumococcal pneumonia. Three of the 24 had the diagnosis established at autopsy; they are excluded in the following discussion as all died of causes apparently unrelated to their pneumonia. Nine of the remaining 21 children had substantial pleural fluid radiologically and were categorized as having pneumococcal empyema because of positive pleural or blood cultures. The remaining 12 children had proved (eight by blood, four by tracheal aspirate) pneumococcal pneumonia, but no evidence of effusion.

The average age of the 12 patients with pneumonia without empyema was 3.3 years, with a range of 5 weeks to 14 years. There were four infants in this group. These children had localized involvement on chest roentgenograms, confined to one or more lobes. None had pneumatoceles. Ten of these children with pneumonia were afebrile within an average of 21 hours

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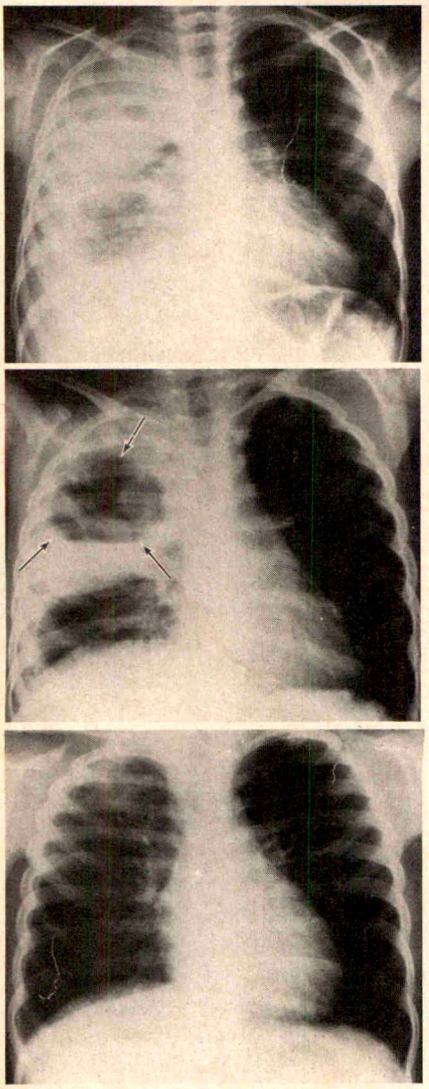

Fig 1.—Case 1. Top, On admission. Center, Pneumatoceles one week later (arrows). Bottom, On follow-up two months later.

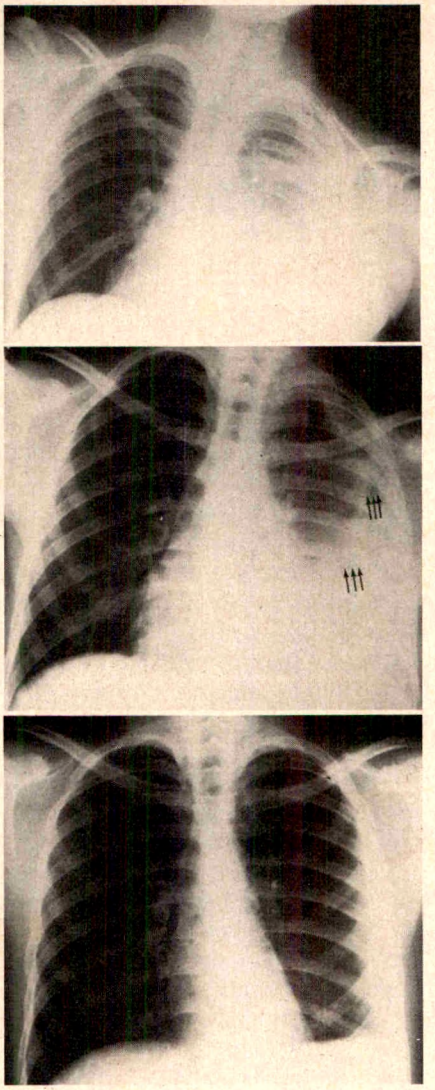

Fig 2.—Case 2. Top, On admission. Center, Pneumatoceles five days later (arrows). Bottom, On follow-up 15 months later.

Patient/Age, yr	Positive Culture
1/7	Pleural
2/12	Pleural, CIE† (antibiotic before arrival)
3/14	Pleural
4/3	Pleural
5/4	Blood
6/3	Pleural
7/5	Pleural
8/4½	Blood
9/12	Pleural

*Still febrile on day of discharge.
†Counterimmunoelectrophoresis.

after initiating appropriate antibiotic therapy. The only two children with pneumonia who were still febrile after 48 hours had underlying disease processes that were believed to contribute to the fever. Radiologically, the degree of lung involvement was much less in this group compared with those with empyema.

The characteristics of the nine children with pneumonia and empyema are summarized in Table 1. The average age was 7.3 years, with a range from 3 to 14 years. There were no infants in this group as compared with the four in the pneumonia without empyema group. All diagnostic cultures were from blood (two) or pleural fluid (six). One of the pleural fluid specimens was negative on culture but positive on CIE. This child had received antimicrobial therapy prior to admission. All of the empyema patients were in a much improved clinical condition (decreased toxicity and respiratory distress) within 24 to 48 hours of appropriate antibiotic therapy, despite persistent high fevers (temperature greater than 38 °C). Repeated pleural fluid or blood cultures were sterile within 24 to 48 hours after the institution of antibiotic therapy in five patients. From time of admission, the average number of days of fever (minimum estimate) was 7.4 days, with a range of two to greater than ten days. Four children were still febrile at the time of discharge from the hospital.

The chest radiologic findings of the empyema patients were extensive on admission, with either total hemithorax or multilobe involvement in five of the nine patients. Extensive pleural fluid accumulations were present in seven of the nine children. Two children had extensive lower lobe involvement with only moderate to minimal pleural fluid. These two patients experienced the shortest febrile period. Five patients' roentgenograms showed evidence of pneumatocele formation during therapy.

Extensive radiologic improvement was usually not apparent for one to two weeks after the initiation of therapy, and pleural thickening was often present for months thereafter.

Patient 1 (Fig 1) demonstrated a large pneumatocele with air fluid levels within the first week of therapy. At that point in therapy, the patient's condition was clinically much improved with sterile chest tube drainage. Therefore, despite the possibility of abscess formation and the continued fever, we elected to treat him conservatively. His chest tube was removed at 48 hours and he continued to improve with oral therapy, with

e 1.—Characteristics of Patients With Empyema

Initial Chest Roentgenogram	Drainage Procedure	Days Until Afebrile	Discharge Roentgenogram				Follow-up Roentgenogram	
			Day	Pneumatoceles	Persistent Infiltrate	Persistent Fluid	Interval	Results
Consolidation in right lung; total opacification	Chest tube for 2 days	6*	6	+	+	+	2 mo	Mild pleural thickening
Consolidation in left lung; total opacification	Chest tube for 3½ days	10	5	+	+	+	2 yr	Mild pleural thickening
Consolidation in left lung; total opacification	Chest tube for 4 days	8	8	+	+	+	9 mo	Slightly elevated left diaphragm; otherwise normal
Consolidation in left lung; total opacification	Thoracentesis	9*	9	—	+	+	1 yr	Normal
Consolidation in left lung; total opacification	None	10*	10	+	+	+	3 yr	Normal
Diffuse left-lung infiltrate; substantial pleural fluid	Chest tube for 1 day	4*	3	—	+	+	3 mo	Normal
Left lower-lobe extensive infiltrate; minimal fluid	Thoracentesis	4	5	—	+	—	7 yr	Normal
Diffuse left-lung infiltrate; free fluid	Bronchoscopy	9	13	—	+	+	. . .	Not available
Right lower-lobe extensive infiltrate; minimal fluid	Thoracentesis	4	5	—	+	—	1 mo	Complete clearing

Table 2.—Pulmonary Function Values*

Patient	Interval From Discharge	FEV, %				Single-Breath Nitrogen Washout, %	% of Predicted Value				
		0.5 s	1 s	2 s	3 s		ERV	FVC	FRC	RV	TLC
1	2 mo	65	83	77	110	<1.0	125	75	141	140	93
2	2 yr	65	90	98	100	<0.5	96	92	93	90	91
4	1 yr†	88	99	99	100	<1.0	100	83	173	237	123
5	3 yr	73	86	90	99	. .	55	76	149	209	105
7	7 yr	59	86	100	100	0.2	61	87	120	209	105
Normal	. . .	>65	>85	>95	>98	<1.5	. . .	. . .	. . .	. . .	. . .

*From Polgar and Promadhat.[19] FEV: indicates forced expiratory volume; ERV, expiratory reserve volume; FVC, forced vital capacity; FRC, functional residual capacity; RV, residual volume; and TLC, total lung capacity.
†Patient's cooperation marginal.

resolution of his apparent intrapulmonary loculation.

Patient 2 (Fig 2) had been hospitalized for four days at another hospital before being transferred to our hospital. On admission, his chest roentgenogram demonstrated multiple pneumatoceles that became more prominent while he was given parenteral therapy. The pleural fluid was culture-negative but CIE-positive for *S pneumoniae*. The patient was in no respiratory distress and clinically doing well at discharge after five days of parenteral therapy, in spite of the failure of chest tubes to adequately drain the loculated pleural effusion. Again, repeated chest roentgenograms demonstrated progressive resolution of fluids, infiltrates, and pneumatoceles.

Only four children were treated with chest tube drainage, the longest for four days. Three children were treated with thoracentesis alone. All had persistent infiltrates and pleural fluid in spite of attempts at drainage, and four had pneumatoceles present at the time of discharge. Follow-up roentgenograms in eight children one month to seven years after discharge demonstrated normal findings in six and minimal residual parenchymal or pleural disease in two.

Table 2 lists the results of pulmonary function tests performed on the five patients available for follow-up investigation. The expected normal values are indicated, as well as the time from discharge to the time of the study. All the children, except patient 2, had some increase in their residual volume. There was, however, no evidence of obstructive airway disease or compromised function by forced expiratory volume studies, single-breath nitrogen washout, or flow-volume loop. All of the children were well, participating in normal activities and with no exercise limitations. None had an increased frequency of school absenteeism (averaging two to three days per school year), illnesses, or pulmonary disease, and none had scoliosis.

COMMENT

Our data suggest that children with severe pneumococcal empyema may be treated with appropriate antibiotics and conservative drainage procedures with good outcome, assuming the causative organism is demon-

strated to be a susceptible *S pneumoniae*. Recent reports of pneumococci resistant to penicillin necessitate a thorough evaluation of all such organisms associated with serious clinical infection.[7] Early chest tube drainage or thoracentesis may relieve respiratory symptoms caused by excessive empyema volume and may reduce the duration of fever, which tends to be prolonged in the presence of persistent fluid. However, these procedures *rarely* eliminate all of the fluid and may be terminated once the child's condition is clinically improved despite prolonged fever, persistent pleural fluid, or the development of pneumatoceles. After resolution of respiratory distress and once oral antibiotics and fluids are tolerated, the patient may be discharged with close follow-up. Subsequent pulmonary function studies and chest roentgenograms have demonstrated no serious abnormalities when this approach is adopted.

Physicians may become concerned when the patient with pneumococcal empyema does not rapidly become afebrile. In an older review of pneumococcal pneumonia (as in the present study), the rapidity of defervescence with appropriate antibiotic therapy was notable.[8] Some authors[9] did state that a prolonged convalescence with persistent empyema could be accompanied by low-grade temperature elevation. In 1944, Tillett et al[8] stated that fever in the patient with pneumococcal empyema is not a reason to change approach or therapy if the patient is demonstrating clinical improvement.

Patients with pneumatoceles have prompted some authors to treat pneumococcal empyema as they do staphylococcal empyema.[10] Very aggressive therapy such as rib resection, open drainage, and decortication was previously recommended for staphylococcal empyema.[1,11,12] However, more recently, other authors have taken a different approach,[5,13,14] stating that not only are there better antistaphylococcal antibiotics available, but the child's ability to resolve a thickened pleura is vastly superior to that of the adult. They point out that if the child's condition is improving clinically, one can wait for weeks or months for the roentgenogram to clear.

Pneumatoceles have not contributed to the morbidity of pneumonia, as noted by Hendren and Haggerty,[15] Ravitch and Fein,[4] and most recently in 1978 by Sullivan et al[16] and Asmar et al.[17]

All nine of the children in the present series were in clinically improved conditions without respiratory distress after 24 to 48 hours of appropriate antibiotic therapy, despite persistent fever and sometimes apparently worsening chest roentgenograms. These patients progressed to complete healing without extensive surgical drainage or prolonged hospitalization. On long-term follow-up, none was left with decreased pulmonary function, impaired thorax growth, or scoliosis. The only serious abnormality in pulmonary function testing was the increased residual volume. This measurement is highly variable and when increased is usually associated with obstructive airway disease. We have no evidence of obstructive disease from the normal forced expiratory volume, single-breath nitrogen washouts, or flow-volume loop studies. In 1966, Groff et al[3] followed up 21 cases of empyema in children caused by a variety of organisms; they found all the children to be asymptomatic with no scoliosis or decrease in exercise tolerance. Although two of the 21 patients received rib resections, the authors stated, "It is our strong feeling that adequate chest tube drainage in children can be obtained without rib resection. It is rare that closed tube drainage needs to be converted to open drainage tube." Pagtakhan and Chernick,[14] in their chapter on the therapy of empyema in children, support this view and state that if the symptoms are relieved after closed drainage the tube can often be removed after 24 hours. Wise et al[18] reviewed 15 patients with staphylococcal pneumonia and empyema treated conservatively. They found that these patients had no increase in illness, no decrease in growth as compared with siblings, and that all their pulmonary functions were normal.

We believe our data support the same conclusion for the treatment of pneumococcal empyema, assuming appropriate antibiotic therapy is selected. The nine children described here responded favorably to conservative therapy despite extensive chest disease, incomplete drainage of pleural fluid, pneumatoceles, and prolonged fever.

John B. Campbell, MD, evaluated the chest roentgenograms. Lynda Gregory helped prepare the manuscript.

References

1. Bechamps GJ, Lynn HB, Wenzl JE: Empyema in children: Review of Mayo Clinic experience. *Mayo Clin Proc* 45:43-50, 1970.
2. Gourlay RH: Staphylococcal pneumonia and empyema in infants and children. *Can Med Assoc J* 87:1101-1105, 1962.
3. Groff DB, Randolph JG, Blades B: Empyema in childhood. *JAMA* 195:572-574, 1966.
4. Ravitch MM, Fein R: The changing picture of pneumonia and empyema in infants and children. *JAMA* 175:1039-1044, 1961.
5. Stiles QR, Lindesmith GG, Tucker BL, et al: Pleural empyema in children. *Ann Thorac Surg* 10:37-44, 1970.
6. Siegel JD, Gartner JC, Michaels RH: Pneumococcal empyema in childhood. *Am J Dis Child* 132:1094-1096, 1978.
7. Dixon JMS, Lipinski AE, Graham MEP: Detection and prevalence of pneumococci with increased resistance to penicillin. *Can Med Assoc J* 117:1159-1161, 1977.
8. Tillett WS, Cambier MJ, McCormack JE: Treatment of lobar pneumonia and pneumococcal empyema with penicillin. *Bull NY Acad Med* 20:142-178, 1944.
9. Reimann HA: *The Pneumonias*. Philadelphia, WB Saunders Co, 1938, chap 3.
10. Smith MHD: Bacterial pneumonias: Gram-positive, in Kendig EL Jr (ed): *Disorders of the Respiratory Tract in Children*, ed 3. Philadelphia, WB Saunders Co, 1977, pp 378-397.
11. Middelkamp JN, Purkerson ML, Burford TH: The changing pattern of empyema thoracis in pediatrics. *J Thorac Cardiovasc Surg* 47:165-173, 1964.
12. Wolfe WG, Spock A, Bradford WD: Pleural fluid in infants and children. *Am Rev Respir Dis* 98:1027-1032, 1968.
13. Light RW: Management of parapneumonic effusions. *Chest* 70:325-326, 1976.
14. Pagtakhan R, Chernick V: Pleurisy and empyema, in Kendig EL Jr (ed): *Disorders of the Respiratory Tract in Children*, ed 3. Philadelphia, WB Saunders Co, 1977, pp 475-487.
15. Hendren WH, Haggerty RJ: Staphylococcic pneumonia in infancy and childhood: Analysis of 75 cases. *JAMA* 168:6-16, 1958.
16. Sullivan D, Fishaut M, Taylor KJW: Diagnostic ultrasound in the management of persistent pleural opacities. *Am J Dis Child* 132:206-207, 1978.
17. Asmar BI, Thirumoorthi MC, Dajani AS: Pneumococcal pneumonia with pneumatocele formation. *Am J Dis Child* 132:1091-1093, 1978.
18. Wise MB, Beaudry PH, Bates DV: Long-term follow-up of staphylococcal pneumonia. *Pediatrics* 38:398-401, 1966.
19. Polgar G, Promadhat V (eds): *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia, WB Saunders Co, 1971.

Behavioral Symptom Substitution in Children Cured of Encopresis

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• **Follow-up data were obtained on 47 children who had been treated for encopresis with an initial catharsis, maintenance laxative therapy, demystification, symptom-related counseling, and close follow-up. Behavioral inventories were used at the beginning of treatment and three years later to determine whether any significant symptom substitution occurred in children cured of encopresis. Little evidence of this was uncovered. There was a comparison of cured and uncured children with respect to behavioral profiles at the start of treatment and three years later. The uncured group showed more aggressive behaviors initially, and also were more socially withdrawn at the start of treatment, although this was not evident three years later. Monitoring of associated behaviors should be an important part of the management of encopresis.**

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Encopresis is a common childhood plight, the optimal management of which is a subject of continuing debate.[1-5] The outcome of treatment is likely to reflect itself not only in bowel function, but also in a child's overall behavior and life adjustment. Therefore, the results of intervention may be seen not merely in the attainment of continence, but also in a wide range of associated behavioral outcomes. The present study was undertaken to determine if children cured of encopresis through a pediatric regimen replaced their bowel symptoms with other maladaptive behaviors following their "cure."

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BACKGROUND

Psychodynamically oriented interpretations of encopresis commonly refer to a child's "need" to be incontinent, implying that the symptom has some utility in the context of disturbed families and problem children. From a therapeutic perspective, it might follow that treatment of family psychopathologic problems must take precedence.[6-8] One might anticipate that merely removing the symptom of encopresis would engender deterioration, or, at least, significant substitution of other maladaptive behaviors. If this were true, one could hypothesize that pediatrically managed children would be in danger of decompensating in other psychological areas following symptomatic relief of their bowel dysfunction.

A previous report described the evaluation of a pediatric treatment program for patients with encopresis at the Children's Hospital Medical Center in Boston.[2] After an initial case analysis using interviews and special questionnaires, the following therapeutic program was implemented: (1) an initial "demystification" or explanation to parents and the child about the cause and apparent pathophysiologic condition culminating in the problem; (2) an explicit effort to alleviate guilt and communicate in a nonaccusatory mode; (3) an initial catharsis during which the child was disimpacted completely with enemas and laxatives. The effectiveness of this procedure was documented by plain x-ray films of the abdomen taken before and after the procedure[9]; (4) maintenance laxative, and/or stool softener therapy for at least six months; (5) a bowel retraining program consisting of twice a day use of the bathroom for ten minutes each time (at the same times each day) reinforced with rewards for children under 8; (6) regular follow-up and monitoring, including availability for phone checks and scheduled return visits to discuss progress, to build rapport, and to deal with concerns related to the bowel problem.

The management program did not

Table 1.—Items On School-Age Behavioral Inventory

Social Withdrawal Behaviors	
Is a "loner"	Prefers adults as friends
Has no "real friends"	Gets picked on
Loses friends easily	Gets jealous easily
Has mostly younger friends	Is slow to make friends
Has mostly older friends	Likes to act like opposite sex
Has mostly friends of opposite sex	Likes to wear clothes of opposite sex
Has no best friend	Constantly fights with brothers/sisters
	Often watches TV alone in afternoon
Antisocial-Aggressive Behaviors	
Tells lies	Destroys objects at home
Steals at home	Destroys objects away from home
Steals away from home	Disobeys adults
Often plays with matches	Acts fearless
Smokes cigarettes	Cheats in games
Uses foul language	Skips school
Bullies other children	Gets in trouble with neighbors
	Cruel to animals
Affective-Dependent Behaviors	
Is moody	Is often sad
Has a bad temper	Tries to sleep with parents
Cries easily	Is often very quiet
Is a worrier	Whines often
Has bad dreams	Has many fears
	Is often tired
Somatic Manifestations	
Too concerned about cleanliness	Sucks thumb
Stutters or stammers	Has nervous twitches
Wets bed or pants often	Complains of feeling ill often
Often has headaches	Has constipation
Soils underwear	Is too neat and orderly
Overeats often	Bites nails

include referral for psychotherapy, surgical evaluation, a barium enema, or a rectal biopsy. Follow-up visits (lasting 30 minutes or less) occurred every four to six weeks during the first six months, and less often after that. They did not include discussions of family problems or other psychodynamic issues apart from those directly related to management of the child's encopresis. Most of the time was spent discussing the problem alone with the child. The parents were invited in toward the end of the session to review medications and to ask questions.

As reported in a previous study, approximately 70% of children achieved a cure within one year of the start of treatment. This was defined as six months without incontinence. Another 25% showed substantial improvement, but still had occasional "accidents." Five percent were noted to be treatment-resistant at the end of a one-year period.[2]

METHODS

The present study concentrated primarily on those youngsters whose fecal incontinence subsided after undergoing pediatric treatment. As part of an initial evaluation, parents were asked to fill out a 53-item school-age behavioral symptom inventory (Table 1). This was part of a comprehensive parent questionnaire for children with encopresis (copies of this questionnaire and its instruction manual are available on request). For this study, the parents completed the same inventory at one and three years after the initiation of treatment. This enabled the investigators to track longitudinally a wide array of behavioral themes.

The behavioral symptom inventory is divided into four categories: social withdrawal behaviors; antisocial-aggressive behaviors; affective-dependent behaviors; and somatic manifestations. Within each category there are 11 to 15 items. Parents are asked to indicate whether an item "definitely applies," "applies somewhat," or "does not apply." They can also check the category "cannot say." Each item is rated with a 0 for "definitely applies," a 1 for "applies somewhat," and a 2 for "does not apply." For each category of behavior, a total score is obtained and divided by the number of items answered. This excludes items in the "cannot say" column. If more than three "cannot say" items were checked, the category is considered unscorable for that child. For each category of behavior a mean score is obtained that ranges from 0 to 2, with higher numbers indicating "better behavior."

In order to standardize the behavioral symptom inventory for this and other studies, a comparison group of 98 children with no known major academic problems was selected from a socioeconomically heterogenous school system in the greater Boston area. The children were of comparable mean age and socioeconomic status, although the comparison group contained a higher proportion of girls (40% vs 21%). Parents were asked to fill out the behavioral inventory for these youngsters. Compliance was greater than 90%. In addition to overall standardization of the inventories, there was scrutiny of the ways in which variations in scores related to sex and age. Statistically significant sex differences were not demonstrable in any behavioral category. Changes with age are reflected in Fig 1. These behavioral inventories are currently under processes of validation on normative samples and in various behavioral and learning problem clinics.

To study behavioral change in children treated for encopresis, questionnaires were mailed three years after the initial visit. Parents were asked to complete the behavioral inventory and to answer questions about the child's current bowel function and academic performance. Approximately 70% returned the forms. This included 36 children who had been cured of encopresis and 11 who had not. Mean behavioral scores were computed for the same group of children at the initial visit and the three-year checkpoint.

RESULTS

Scores for the behavioral categories were calculated. Figure 1, top left, shows a comparison of social withdrawal behaviors. The solid line at the top reflects the mean comparison group scores at each age. Although the comparison group were roughly evenly distributed by sex, the encopresis groups were predominantly male. Because comparison group data showed no statistically significant sex differences, sexes were combined for this analysis.

Beginning at age 7, there was a major difference in social withdrawal behaviors between the comparison group and the children before treatment. There were no significant differences at the ages of 5 and 6. With age it is clear and not surprising that social withdrawal tended to increase

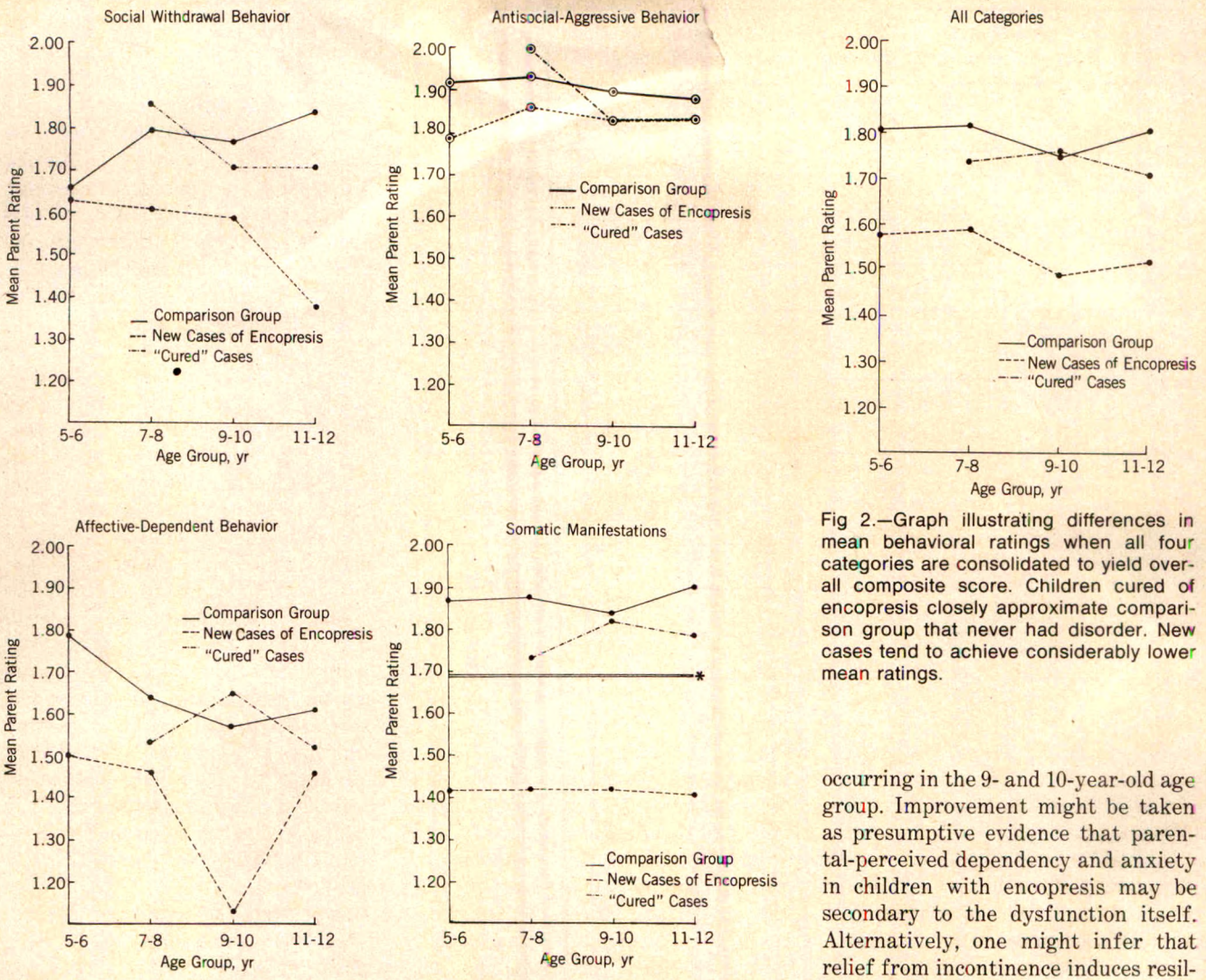

Fig 1.—Four graphs illustrate mean behavioral scores in each of four categories at specific age levels. In each, comparison group without encopresis is contrasted to children at start of treatment program and to those same youngsters three years later. Significant differences emerge, suggesting behavioral improvement after symptom relief. Mean rating based on constipation and soiling items without other somatic symptoms (asterisk).

Fig 2.—Graph illustrating differences in mean behavioral ratings when all four categories are consolidated to yield overall composite score. Children cured of encopresis closely approximate comparison group that never had disorder. New cases tend to achieve considerably lower mean ratings.

in children with encopresis. Peer and adult ridicule and rejection over time may have fostered this process. The middle line in Fig 1, top left, traces a statistically significant improvement in social integration among youngsters cured of encopresis. There was a trend away from isolation toward more engagement in peer and family interaction.

Figure 1, top right, is a comparison of antisocial-aggressive behaviors. Here it can be seen that antisocial-aggressive traits were not characteristic of new encopretic children at any age. Consequently, one discerns little alteration in these scores before and after treatment.

The affective-dependent behavior patterns are shown in Fig 1, bottom left, where some of the most dramatic differences are seen. These behaviors are thought to reflect signs of depression, affective lability, and anxiety. At all ages, there were significant differences between the pretreatment and the comparison group. Following the conquest of encopresis, patients approximated the comparison group. One can see particularly large changes occurring in the 9- and 10-year-old age group. Improvement might be taken as presumptive evidence that parental-perceived dependency and anxiety in children with encopresis may be secondary to the dysfunction itself. Alternatively, one might infer that relief from incontinence induces resiliency in affective areas and personality development. At any rate, it would appear that the cure of encopresis exerted its major behavioral effects on the alleviation of chronic anxiety, dependency, and incipient depression.

Figure 1, bottom right, traces somatic manifestations. Since several of the items on the inventory relate directly to symptoms such as constipation and soiling, these in themselves would lower scores in this area. In Fig 1, bottom right, the double line with an asterisk represents the level one would see in a child with encopresis who had only abdominal symptoms. Untreated cases of encopresis scored on the average well below the threshold, indicating that affected youngsters tended also to have extraabdominal somatic symptoms. There was considerable resiliency in the group

Table 2.—Mean Behavioral Rating Scores: Comparison of Ultimately Cured and Uncured Groups, at Start of Treatment

Category	Comparison Group Mean (SD)	Cured Group (N = 31) Mean (SD)	Uncured Group (N = 11) Mean (SD)
Social withdrawal	1.79 (0.26)	1.60 (0.24)	1.44 (0.29)
Antisocial-aggressive	1.91 (0.14)	1.82 (0.11)	1.46 (0.13)
Affective-dependent	1.39 (0.31)	1.39 (0.27)	1.40 (0.24)
Somatic manifestations	1.87 (0.13)	1.41 (0.18)	1.46 (0.19)

Table 3.—Mean Behavioral Rating Scores: Comparison of Cured and Uncured Groups After Three Years

Category	Comparison Group Mean (SD)	Cured Group (N = 36) Mean (SD)	Uncured Group (N = 11) Mean (SD)
Social withdrawal	1.79 (0.26)	1.71 (0.29)	1.83 (0.33)
Antisocial-aggressive	1.91 (0.14)	1.84 (0.17)	1.64 (0.26)
Affective-dependent	1.39 (0.31)	1.61 (0.21)	1.36 (0.24)
Somatic manifestations	1.87 (0.13)	1.76 (0.24)	1.47 (0.19)

cured of encopresis, with no evidence of generalized substitution of new physical symptoms.

In Fig 2, all categories of behavior were collapsed into one composite score and a behavioral mean obtained for each age group. This illustrates again that untreated children with encopresis had the lowest scores, while cured children closely approximated the comparison group, especially at ages 9 and 10.

An effort was made to characterize behavioral symptom patterns in the 11 children who were *not* cured. Table 2 compares mean behavioral scores at the start of treatment for those who were ultimately cured and for those who were treatment-resistant after three years. Statistically significant differences were evident in social withdrawal tendencies and antisocial-aggressive behaviors. Such propensities toward social maladaptation might be considered flags of poor prognosis. There were no significant differences in affective-dependent behaviors or in somatic manifestations.

Comparison between cured and uncured patients at the three-year checkpoint are seen in Table 3. Surprisingly, the uncured group made substantial gains in social adaptation. It may be that the alleviation of guilt, the process of demystification, and the supportive aspects of management were therapeutic even though bowel symptom treatment had not succeeded. The uncured children tended to score better in these areas than did untreated patients at the same ages. The latter showed little change in affective-dependent behaviors and somatic manifestations.

The major group differences in somatic manifestations reflected largely relief of the encopresis-related symptoms. The cured group showed considerable improvement in affective-dependent traits, while the uncured did not shed the signs of anxiety, depression, and excessive dependence. From these data, there is no way to determine whether the persistence of affective-dependent behaviors in the uncured group was a reason for their treatment resistance or the result of continuing poorly controlled incontinence.

As part of the initial and follow-up evaluation of children in this study, parents were asked to rate school performance. For purposes of this report, three areas will be described: reading, spelling, and arithmetic. Each child's academic attainment was rated on a scale from 0 to 3, with 0 representing failure and 3 advanced achievement. A total score was obtained for performance in all three areas before and after treatment, ranging from 0 to 9. The mean academic score for children cured of encopresis was 6.10 at the start of treatment, and 5.71 at the three-year follow-up assessment, indicating a statistically insignificant decline in perceived academic performance. The initial academic ratings of uncured children was substantially lower, 5.10. However, after three years, the uncured children showed a slight improvement in academic performance (to a rating of 5.50). To evaluate this further, an individual case analysis was undertaken. Four youngsters from the cure group actually experienced a decline of two or more points in perceived reading achievement; 32 showed no significant changes with only minor fluctuations in academic performance. Of the 11 in the uncured group, none showed deterioration, while two showed significant improvement.

In general, the treatment of encopresis was associated with little impact on school performance. However, it should be emphasized that these scores represented parent perceptions rather than direct teacher ratings or standardized test results. Moreover, there were no available normative data on the age fluctuations of parent-perceived school performance in nonencopretic children.

Although there was overall parent-perceived improvement in behavior among youngsters who had been cured of encopresis, an effort was made to determine if any of the children suffered major behavioral deterioration following cure. To determine this, individual case analyses were performed. Eight of the 36 cured children were noted to have substituted one or more entirely new symptoms during treatment. In two of these, the new symptom was nail-biting. In two others, the only new trait was a tendency to be slow to make friends.

Another child was said to undergo prolonged periods of sadness, but this youngster had endured the death of his father. Thus, there was no consistent trend toward acquisition of any specific symptom or cluster in the cured group. In no case did a child's condition deteriorate to the point where he or she was hospitalized for emotional difficulties, arrested by the police, suspended from school, or said to have developed highly troublesome new symptoms such as fire-setting, school phobia, or stealing. There were no intercurrent divorces or marital separations in the cure group.

COMMENT

It is clear from this study that encopresis is seldom an isolated symptom. Bowel incontinence commonly is clustered with other somatic symptoms, with social withdrawal, with affective changes, and with increasing dependency. The high prevalence of associated behavioral symptoms may either be secondary to despair over poor bowel control or the product of the same forces that lead to encopresis. Regardless of their sources, it is clear that such behaviors need to be monitored as an integral part of treatment outcome.

This study offers evidence that the pediatric cure of encopresis is unlikely to result in a major deterioration of behavior. In fact, relief of incontinence was associated with a generalized improvement in the traits surveyed.

There is a need to interpret these findings with some caution: The children studied were likely to have had more severe symptoms of encopresis than those encountered in a primary care setting; many of them had been managed unsuccessfully in the community, and were referred to the medical center for specialized evaluation and higher intensity intervention.[10] Furthermore, since these youngsters were referred to a pediatric rather than a child psychiatric clinic, one might question whether they had less associated psychopathologic problems than children undergoing psychotherapy or psychiatric evaluation for encopresis. It would be important to study differences between encopretic children in pediatric care and those in psychiatric settings. It would be useful to compare those receiving pediatric treatment for encopresis to youngsters receiving psychotherapy and to children receiving pediatric treatment for other chronic disorders of development or function.

In this study, there may have been "halo effects" introduced by parents who were euphoric over improved household odors and an end to soiled underpants buried in the garden! Future behavioral outcome studies need to examine the child directly, measuring such factors as self-esteem and affect. Despite the limitations of reported data, behavioral inventories can be helpful to pediatricians in observing the range of secondary effects of childhood functional disorders, in assessing mental health, and in evaluating the broad functional outcomes of any intervention. The utilization of such tools can be useful, both from an investigational and clinical standpoint. Information so collected can be relevant in mapping management strategies, in assessing the likelihood of compliance, in determining the need for other interventions, and, to some extent, in predicting outcome.

We believe that this study further justifies a focused, supportive, and tenacious pediatric role in the management of the symptoms of encopresis. It tends to refute the notion that an exclusively pediatric effort concentrated on a functional problem for which help was sought is likely to result in deterioration in other areas of behavior. Psychotherapy or a family dynamics orientation certainly has a place in select cases in conjunction with pediatric treatment. In general, however, comprehensive pediatric management and directive counseling can have beneficial effects in helping children recover from incontinence and from its galaxy of associated maladaptive behaviors.

Tom Ferb, PhD, assisted in the statistical analyses, and Linda Evans helped prepare the manuscript.

References

1. Berg I, Jones KV: Functional fecal incontinence in children. *Arch Dis Child* 39:465-472, 1964.
2. Levine MD, Bakow H: Children with encopresis: A study of treatment outcome. *Pediatrics* 58:845-852, 1976.
3. Davidson M, Kugler MM, Bauer CH: Diagnosis and management in children with severe and protracted constipation and obstipation. *J Pediatr* 62:261-275, 1963.
4. Silber DL: Encopresis, discussion of etiology and management. *Clin Pediatr* 8:225-231, 1969.
5. Fitzgerald JF: Difficulties with defecation and elimination in children. *Clin Gastroenterol* 6:283-297, 1977.
6. Coekin M, Gairdner D: Fecal incontinence in children. *B Med J* 2:1175, 1960.
7. Pinkerton P: Psychogenic megacolon in children: The implications of bowel negativism. *Arch Dis Child* 33:371-380, 1958.
8. Easson WM: Encopresis—psychogenic soiling. *Can Med Assoc J* 82:624-627, 1960.
9. Barr RG, Levine MD, Wilkinson RH, et al: Occult stool retention: A clinical tool for its evaluation in school-aged children. *Clin Pediatr* 18:674-684, 1979.
10. Levine MD: Children with encopresis: A descriptive analysis. *Pediatrics* 56:412-416, 1975.

Bacteremias due to *Haemophilus influenzae* and *Streptococcus pneumoniae*

Their Occurrence and Course in Children With Cancer

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• **Nine *Haemophilus influenzae* and 24 *Streptococcus pneumoniae* bacteremias occurring in children with cancer during the years 1968 to 1977 were reviewed. The number of bacteremias due to these organisms remained relatively constant, in contrast with a sharp decrease in bacteremias caused by other organisms during this period. The highest incidence of bacteremia occurred in patients with acute leukemias and the lowest incidence in patients with solid tumors. Twenty-seven of 33 episodes occurred while patients were receiving chemotherapy. Nine bacteremias were fatal, but concurrent or superinfections contributed to death in six of these. Children with cancer who are receiving chemotherapy seem to be at higher risk of bacteremia and meningitis due to *H influenzae* and *Strep pneumoniae* than are normal children. New approaches to the prevention of these infections, such as the use of bacterial polysaccharide vaccines, deserve investigation.**

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Patients with cancer frequently suffer serious infections, most often due to enteric Gram-negative bacteria and *Staphylococcus aureus*.[1] A review of positive blood cultures from pediatric cancer patients at the Children's Hospital Medical Center during the past ten years disclosed a sharp decrease in the incidence of all bacteremias, but a relatively constant number of bacteremias caused by the encapsulated pyogens *Haemophilus influenzae* and *Streptococcus pneumoniae*. These two organisms now account for a substantial proportion of the positive blood cultures in these patients. I have, therefore, reviewed the clinical features of bacteremias caused by these organisms and calculated disease-specific incidence rates with a view to identifying high-risk patients who are likely to benefit from immunization with pneumococcal and *H influenzae* type b polysaccharide vaccines.

MATERIALS AND METHODS

Bacteremias were ascertained by reviewing records of positive blood cultures in the clinical bacteriology laboratory of Children's Hospital Medical Center, Boston. The following criteria were adopted to distinguish bacteremias from contamination: blood cultures yielding *Staph aureus*, β-hemolytic streptococci, *Strep pneumoniae*, *H influenzae*, *Neisseria meningitidis*, Enterobacteriaceae, *Pseudomonas aeruginosa*, and other nonfermenting, Gram-negative rods were assumed to represent bacteremia; blood cultures yielding *Staph epidermidis*, α-hemolytic streptococci, bacillus species, and diphtheroids were considered to be contaminants when present in a single blood culture, and indicative of bacteremia when present in two or more blood cultures.

Blood cultures were inoculated into trypticase soy broth and thioglycollate broth from 1968 to 1973, into dextrose phosphate broth and thioglycollate broth from 1973 to 1975, and into *Brucella* broth and Columbia broth from 1975 to 1977. Prior to 1973, blood cultures were not routinely subcultured, but Gram stained before discarding the bottles after five to seven days. From 1973 to 1977, subcultures were performed onto chocolate agar after 24 hours and after seven days. Bacterial isolates were identified using standard bacteriologic techniques. *Haemophilus influenzae* was serotyped by agglutination with type-specific antisera obtained from Burroughs-Wellcome Laboratories, Research Triangle Park, NC, and *Strep pneumoniae* was serotyped at the Massachusetts State Laboratory, Boston, using the Quellung reaction with typing sera provided by the Center for Disease Control, Atlanta.

Census figures according to underlying illness were obtained from the computer records of the Sidney Farber Cancer Institute, Boston. The number of patient-years was calculated using the assumption that patients who were diagnosed or who died in a given year were observed for six months during that year, as follows: number of patient-years equals the number of survivors from previous years plus the number of deaths divided by two plus the number of new diagnoses divided by two. The total number of patients seen was calculated by adding the number of patients followed up in January 1968 to the number of patients diagnosed in each subsequent year. Children seen only in consultation or unavailable for follow-up were excluded from the calculations.

RESULTS

The number of bacteremias due to all organisms and due to *H influenzae* and *Strep pneumoniae* during each year from 1968 to 1977 is given in Table 1. The total number of bacteremias had decreased approximately threefold, whereas the number of bacteremias caused by *Strep pneumoniae* has remained relatively constant. Bacteremias due to *H influenzae* were observed only in the second five years of the survey. This may have resulted from the fact that routine subcultures onto chocolate agar were not performed prior to 1973. As a consequence, *H influenzae* bacteremias may have been missed because this organism typically produces little visible change in blood culture bottles.

Table 1.—Number of Bacteremias Seen Each Year due to *Haemophilus influenzae* and *Streptococcus pneumoniae*

	No. of Bacteremias by Etiology		
Year	All Organisms	*H influenzae*	*Strep pneumoniae*
1968	73	. . .	2
1969	75	. . .	4
1970	74	. . .	2
1971	53	. . .	3
1972	37	. . .	2
1973	39	2	2
1974	38	4	3
1975	16	2	2
1976	25	1	2
1977	22	0	2
Total	**452**	**9**	**24**

The rate of accrual of new patients during the study period was relatively constant, averaging 47 patients/year for acute lymphocytic leukemia, 9.2/year for acute myelocytic leukemia, 12/year for Hodgkin's disease, and 73/year for solid tumors. However, the number of deaths decreased dramatically, from 106/year during the first three years of the study to 54/year during the last three years. The decline in the number of deaths, which was especially prominent in patients with acute lymphocytic leukemia, reflects improved treatment rather than a declining patient population. The increased survival resulted in an increasing number of patient-years observed each year during the ten-year period, but an increasing proportion of these patient-years is comprised of long-term survivors who are no longer receiving therapy.

Table 2 gives the incidence rates of bacteremia, expressed as the number per 100,000 patients per year, according to underlying malignancy. The incidence rates for *H influenzae* bacteremia were based only on the number of patient-years observed during the last five years of the survey because the bacteriologic methods were not adequate to ascertain all cases prior to 1973. Although the number of pneumococcal bacteremias per year remained relatively constant (Table 1), the incidence decreased from 956/100,000 patient-years for the period 1968-1972 to 388/100,000 patient-years for the period 1973-1977. This decreased incidence may reflect the fact that an increasing number of patients were not receiving chemotherapy and therefore were at low risk.

Table 3 gives the epidemiologic features of bacteremias due to *H influenzae* and *Strep pneumoniae*. A child with neuroblastoma had three episodes of *H influenzae* type b bacteremia. The first episode, occurring at the time of diagnosis when the child was 15 months old, was associated with otitis media. The patient's condition responded promptly to treatment with intravenous chloramphenicol sodium succinate followed by ampicillin sodium. Four weeks later, while the patient was receiving oral ampicillin and was myelosuppressed from her first course of chemotherapy, pneumonia and bacteremia developed due to *H influenzae* type b resistant to ampicillin. This illness responded promptly to treatment with chloramphenicol. Thirteen months later, meningitis and pneumonia developed due

Table 2.—Incidence of *Haemophilus influenzae* and *Streptococcus pneumoniae* Bacteremias in Children With Various Malignancies Seen Between 1968 and 1977

Disease	No. of Patients,* 1968-1977	No. of Patient-Years*		No. of Episodes		Incidence†	
		1968-1977	1973-1977	*H influenzae*	*Strep pneumoniae*	*H influenzae*, 1973-1977	*Strep pneumoniae*, 1968-1977
Acute lymphocytic leukemia	535	1,126.5	718.5	4	15	557	1,332
Acute myelocytic leukemia	113	135.5	59.5	1	5	1,681	3,690
Hodgkin's disease	129	579.5	377	1	(1)‡	265	172
Solid tumors	784	2,354	1,681	3§	4	178	170
Total	**1,561**	**4,196**	**2,836**	**9**	**24**	**317**	**596**

*See text for method of calculation.
†Per 100,000 patient-years.
‡In one patient who had completed therapy for Hodgkin's disease, acute myelocytic leukemia developed.
§Three episodes of *H influenzae* type b bacteremia occurred in one patient (see text).

to *H influenzae* type b sensitive to ampicillin.

As expected, the age of patients with *H influenzae* bacteremia was lower than that of patients with pneumococcal bacteremia. However, only one patient was younger than 2 years and three patients were older than 5 years (9, 9, and 18 years).

Twenty-seven of 33 bacteremias occurred in patients receiving active therapy, four prior to therapy and two after completion of therapy. Patients with pneumococcal bacteremias were more often in relapse and profoundly granulocytopenic.

Table 3.—Demographic and Epidemiologic Features of Bacteremias due to *Haemophilus influenzae* and *Streptococcus pneumoniae*

	*H influenzae**	*Strep pneumoniae*†
No. of episodes (patients)	9 (7)	24 (22)
Age, yr median (range)	3 (1-18)	9 (2-23)
Sex, M/F	4/3	14/8
Stage of therapy		
Before treatment	1	3
Active treatment‡	7	20
After treatment	1	1
Splenectomy	1	1
Disease active or in relapse	1	17
Multiple chemotherapy regimens	2	17
Peripheral granulocyte count, cu mm		
>1,000	7	4
100-1,000	2	4
<100	0	16
Nosocomial (>48 hr after admission)	1	1
Season		
October to March	6	15
April to September	3	9

*Eight episodes were *H influenzae* type b, and one was type c.

†Ten strains isolated from 1973 to 1977 were serotyped and were as follows: type 14, three strains; type 23, two strains; type 6, two strains; and types 8, 18, and 33, one strain each (Danish nomenclature).

‡Defined as treatment for cancer during the six weeks before the episode.

Table 4.—Clinical and Bacteriologic Features of Bacteremias due to *Haemophilus influenzae* and *Streptococcus pneumoniae*

	H influenzae	*Strep pneumoniae*
Initial temperature, °C median (range)	39² (38-41²)	39⁷ (38-40⁸)
Prolonged fever*	1	6
Concurrent or superinfection	1	8
Site		
Meningitis	1 (1)†	4 (4)
Pneumonia	4 (2)	6 (1)
Otitis	4 (0)	5 (0)
Sinusitis	3 (1)	5 (0)
Pharyngitis	2 (0)	2 (1)
Conjunctivitis	1 (0)	0
No focus‡	2	11
Outcome		
Infection resolved	7	17
Died of *H influenzae* or *Strep pneumoniae* infection	1	2
Died of concurrent or superinfection§	1	5

*Defined as a temperature of 38 °C or greater for five days.

†Numbers in parentheses indicate the number of positive cultures from that site.

‡Rhinitis, oral mucositis, abdominal pain, and diarrhea were not considered foci for bacteremia. One patient with pneumococcal bacteremia had a dental abscess. Pharyngitis was never the sole focus of bacteremia.

§Rectal abscess, two patients; polymicrobial bacteremia, two; disseminated candidiasis and aspergillosis, two.

The clinical features of the bacteremias are given in Table 4. Pneumococcal bacteremias were associated with higher and more prolonged fever. The sites of infection were frequently minor or occult. Only one of nine episodes of *H influenzae* and four of 24 episodes of pneumococcal bacteremia were associated with meningitis. Most of the mortality associated with these infections was related to concurrent infections or superinfections with other organisms. In only three patients did death result primarily from infection by *H influenzae* or pneumococcus. Two of these patients had undergone splenectomy for staging of Hodgkin's disease: the first was an 18-year-old man in whom pneumocystis pneumonia developed one month after completing chemotherapy and total nodal irradiation for stage IIIB Hodgkin's disease. After his condition responded to a 12-day course of pentamidine isothiocyanate, rapidly progressive pneumonia and bacteremia developed due to *H influenzae* type b, and he died within 24 hours. The second patient was a 23-year-old woman in whom acute myelocytic leukemia developed three years after completing total nodal irradiation and chemotherapy for Hodgkin's disease. During initial therapy, pneumonia and bacteremia developed due to pneumococcus type 8 and she died within 24 hours with disseminated intravascular coagulation. A third patient with acute lymphocytic leukemia died of a cardiorespiratory arrest shortly after an intrathecal penicillin injection on the fourth day of treatment for pneumococcal meningitis.

COMMENT

During the ten years surveyed, the number of bacteremias in our pediatric cancer patients has declined markedly. Several factors may have contributed to this decrease. Therapeutic advances in the chemotherapy of acute lymphocytic leukemia, partic-

ularly the introduction of combination chemotherapy in 1972, resulted in decreased drug toxicity, fewer relapses, and enhanced survival. The prompt institution of empiric, broad-spectrum antibiotic therapy in cancer patients who were febrile and granulocytopenic may also have prevented bacteremias or prevented their recognition.

Despite the decrease in all bacteremias, the number caused by *H influenzae* and pneumococcus has remained relatively constant. As a consequence, the proportion of bacteremias caused by these organisms has increased from 3.6% during the first three years to 14.3% during the last three years of this review. Proportions of bacteremias due to these organisms, ranging from 6% to 12%, have also recently been reported from other pediatric oncology units.[2-4]

The disease-specific incidence rates were highest in patients with acute leukemias and lowest in those with solid tumors (Table 2). Only two episodes occurred in patients who had undergone splenectomy for Hodgkin's disease; however, both were rapidly fatal. Several factors should be kept in mind when interpreting the bacteremia rates in Table 2. The true incidence may have been underestimated because episodes of infection diagnosed and treated at other hospitals could not be ascertained. Furthermore, the rates were calculated using patients followed up both during and after cancer therapy. Since only two bacteremias occurred after patients had completed treatment, incidence figures during active therapy would be even higher than indicated, especially for solid tumors. On the other hand, the assiduous investigation of febrile episodes in cancer patients may enhance the detection rate of transient bacteremias. Both *H influenzae* and *Strep pneumoniae* may be grown from the blood of febrile children without malignancy who are seen in the outpatient setting.[5]

The incidence of bacteremias due to these organisms in the general population is unfortunately not available for comparison. However, the incidence of meningitis was recently reported by the Center for Disease Control to be 1.24/100,000 population/year for *H influenzae* and 0.6/100,000/year for *Strep pneumoniae*. The corresponding incidence rates in children younger than 2 years of age were 16 and 1/100,000/year.[6] In addition to the five patients with bacteremic meningitis described in this report, we observed six patients with nonbacteremic meningitis, five due to *H influenzae* type b and one due to *Strep pneumoniae*. Thus, the incidence of meningitis in these cancer patients followed up for a total of 4,196 years (Table 2) was 143/100,000 patient-years for *H influenzae* and 119/100,000 patient-years for *Strep pneumoniae*. These incidence rates are substantially higher than those for the general population and even those for children younger than 2 years of age.

Although *H influenzae* type b and *Strep pneumoniae* are both encapsulated pyogens and cause a similar spectrum of diseases in normal children, striking differences between the epidemiologic features of the infections were found in immunocompromised patients (Table 3). Pneumococcal bacteremia typically occurred in children with acute leukemia in relapse, who had received several different chemotherapy regimens, and who were profoundly granulocytopenic from recent chemotherapy. In contrast, *H influenzae* bacteremia occurred in children whose underlying disease was in remission, who were receiving maintenance chemotherapy, and who had adequate numbers of granulocytes.

Children with pneumococcal bacteremia tended to have higher and more prolonged fever, a higher incidence of associated infections, and a higher mortality than did those with *H influenzae* bacteremia (Table 4). These differences probably reflect differences in the severity of the underlying illness rather than differences in pathogenicity of these organisms. Most deaths in both groups occurred in profoundly granulocytopenic patients and were related to concurrent infections or to superinfections with other bacteria or fungi.

The majority of recognized foci of infection were associated with the respiratory tract. Only one of the nine *H influenzae* bacteremias in this series was associated with a meningeal focus, compared with 50% of *H influenzae* bacteremias in the general pediatric population.[7,8] Two of nine (22%) *H influenzae* and 11 of 24 (46%) *Strep pneumoniae* bacteremias had no apparent focus of infection. Folland et al[9] also noted that a high proportion (40%) of pneumococcal bacteremias in cancer patients had no focus of infection, and that younger patients were particularly likely to have no apparent source. On the other hand, Burke et al noted that only 15 of 111 (14%) pneumococcal bacteremias in normal children had no focus of infection.[10] Seven of the 13 bacteremias of unknown source in the present series were associated with symptoms of gastrointestinal toxicity (oral mucositis, vomiting, abdominal pain, or diarrhea) and 12 of 13 with granulocytopenia. Chemotherapy-induced mucosal damage may have permitted these pathogens to invade the blood stream without causing a localized focus of infection. Another possibility is that a localized focus was present but unrecognized because of a decreased inflammatory response.

Whether a diminished concentration of specific antibody is involved in the pathogenesis of these infections is not known. In patients receiving chemotherapy for acute leukemia, hypogammaglobulinemia does develop,[11] and patients who have completed intensive chemotherapy for Hodgkin's disease have decreased levels of specific antibody to the capsular polysaccharides of *H influenzae*[12] and *Strep pneumoniae*.[13]

The high incidence of infections with *Strep pneumoniae* and *H influenzae* suggests that children with cancer are an important target population for bacterial polysaccharide vaccines prepared from these organisms. All but one of the children reviewed were older than 2 years and thus theoretically able to respond to polysaccharide vaccines. If effective, the currently licensed pneumococcal vaccine would have protected nine of ten children whose strains were typed in this series, and 36 of 52 patients (69%) in Folland's series. A vaccine

against *H influenzae* type b might also have prevented eight of the nine episodes of bacteremia with this species.[14] Since most episodes of bacteremia occurred during active anticancer therapy, immunization should optimally be given at diagnosis or early during treatment. This approach is not without risk since the administration of antigen concurrently with chemotherapy may induce tolerance rather than an immune response.[15] Therefore, immunization of cancer patients cannot be routinely recommended until additional studies show that they can develop an adequate antibody response and can maintain antibody levels during prolonged chemotherapy. Ultimately, it would also be desirable to demonstrate protective efficacy in this population.

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Nonproprietary Name and Trademarks of Drug

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection.*

References

1. The EORTC International Antimicrobial Therapy Project Group: Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. *J Infect Dis* 137:14-29, 1978.

2. Chilcote RR, Baehner RL: Septicemia in association with acute lymphocytic leukemia. *J Pediatr* 94:715-718, 1979.

3. DeClerck Y, DeClerck D, Rivard GE, et al: Septicemia in children with acute leukemia. *Can Med Assoc J* 118:1523-1526, 1978.

4. Favor LF, Tarpay M, Blackstock R: Septicemia in children with cancer. *Southern Med J* 72:132-135, 1979.

5. Teele DW, Pelton SI, Grant MJA, et al: Bacteremia in febrile children under 2 years of age: Results of cultures of blood of 600 consecutive febrile children seen in a "walk-in" clinic. *J Pediatr* 87:227-230, 1975.

6. Surveillance summary: Bacterial meningitis and meningococcemia: United States, 1978. *Morbid Mortal Weekly Rep* 28:277-279, 1979.

7. Todd JK, Bruhn FW: Severe *Haemophilus influenzae* infections. *Am J Dis Child* 129:607-611, 1975.

8. McGowan JE, Jr, Klein JO, Bratton L, et al: Meningitis and bacteremia due to *Haemophilus influenzae:* Occurrence and mortality at Boston City Hospital in 12 selected years, 1935-1972. *J Infect Dis* 130:119-124, 1974.

9. Folland D, Armstrong D, Seides S, et al: Pneumococcal bacteremia in patients with neoplastic disease. *Cancer* 33:834-849, 1974.

10. Burke JP, Klein JO, Gezon HM, et al: Pneumococcal bacteremia. *Am J Dis Child* 121:353-359, 1971.

11. Ragab AH, Lindqvist KJ, Vietti TJ, et al: Immunoglobulin pattern in childhood leukemia. *Cancer* 26:890-894, 1970.

12. Weitzman SA, Aisenberg AC, Siber GR, et al: Impaired humoral immunity in treated Hodgkin's disease. *N Engl J Med* 297:245-248, 1977.

13. Siber GR, Weitzman SA, Aisenberg AC, et al: Impaired antibody response to pneumococcal vaccine following treatment for Hodgkin's disease. *N Engl J Med* 299:442-448, 1978.

14. Smith DH, Peter G, Ingram DL, et al: Responses of children immunized with the capsular polysaccharide of *Hemophilus influenzae,* type b. *Pediatrics* 52:637-644, 1973.

15. Hultin MB, Shapiro SS, Bowman HS, et al: Immunosuppressive therapy of factor VIII inhibitors. *Blood* 48:95-108, 1976.

Porencephaly From Periventricular Intracerebral Hemorrhage in a Premature Infant

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• **In two thirds of the premature infants who survived large periventricular intracerebral hemorrhage, a porencephalic cyst developed at the site of parenchymal hemorrhage. The porencephaly seems to develop as a result of local parenchymal destruction by the hemorrhage itself. These cysts can occur in the absence of posthemorrhagic hydrocephalus or increased intracranial pressure. Three of four infants who were observed for at least five months had lateralized motor deficit that corresponded to the cyst.**

(*Am J Dis Child* 134:673-675, 1980)

Cavitations within the cerebral hemisphere may be the result of a developmental aberration or an injury from a variety of sources. The term schizencephaly is used for the former lesions.[1] The destructive lesions are designated by a variety of terms, but encephaloclastic porencephaly (hereafter referred to as porencephaly) is the most appropriate, especially for single, cystic cerebral lesions. Porencephaly may result from diverse destructive influences, occurring usually in the prenatal or early neonatal period, and consisting most commonly of vascular occlusion of hypoxic-ischemic insult.[2,3] Causes cited less commonly include focal encephalitis,[4,5] trauma,[6] and ventricular puncture.[7]

We believe that the role of periventricular intracerebral hemorrhage in the genesis of this lesion is greater than previously recognized. Thus, the complex of periventricular intracerebral-intraventricular hemorrhage has been shown recently to be a very frequent lesion in the premature infant.[8,9] The hemorrhage originates in the periventricular germinal matrix and usually ruptures into the ventricular system.[10] However, extension into the cerebral white matter is not unusual and may result in a large intracerebral hematoma. We have documented recently the evolution of such an intracerebral hematoma into a porencephalic cyst in five infants.

REPORT OF CASES

Case 1.—An infant was born after a 32-week gestation. Spontaneous labor was halted with terbutaline sulfate, but profuse vaginal bleeding associated with a decreasing maternal hematocrit reading necessitated a cesarean section. Birth weight was 1,780 g and the Apgar scores at one and five minutes were 4 and 6, respectively. Severe respiratory distress developed in the delivery room and eventually required assisted ventilation. On the third day of life, the CSF was grossly bloody with a hematocrit reading of 8% and a protein concentration of 384 mg/dL. Computerized tomography (CT) the next day demonstrated an intraventricular hemorrhage (Fig 1). Progressive ventricular dilation developed despite daily lumbar punctures. The initiation of oral glycerin therapy resulted in stabilization of ventricular size. At 5 months of age, developmental progress seems normal and there are no focal deficits. Follow-up CT scans showed the development of a right frontal porencephalic cyst (Fig 2).

Case 2.—An infant was born after a 34-week gestation complicated by maternal ingestion of birth control pills for the first 4½ months. Spontaneous labor was not halted by terbutaline and the infant was delivered by cesarean section. Birth weight was 1,880 g and Apgar scores at one and five minutes were 9 and 10, respectively. Severe respiratory distress developed in the first 24 hours and required ventilatory assistance. On the third day of life, the CSF contained 6,400/cu mm RBCs and a protein concentration of 900 mg/dL. Alternate-day lumbar punctures were performed and on postnatal day 18 a CT scan showed moderate ventricular dilation and a right frontal porencephaly. Progressive ventricular dilation occurred despite glycerin therapy and a ventriculoperitoneal shunt was placed at 4 months of age. The child's psychomotor development was delayed and he had a left hemiparesis with greater involvement of the upper extremity. Increasing congestive heart failure secondary to bronchopulmonary dysplasia resulted in death at age 14 months. Postmortem examination showed a large, porencephalic cyst in the right frontal region (Fig 3).

Case 3.—A female infant was born after a 30-week gestation. Birth weight was 1,400 g and Apgar scores at one and five minutes were 4 and 6, respectively. By 3

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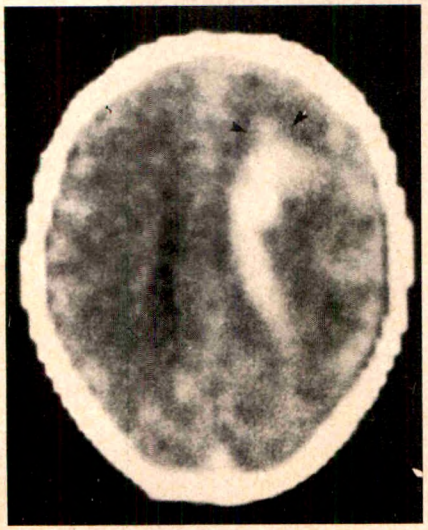

Fig 1.—Hemorrhage in right lateral ventricle with intraparenchymal extension (arrowheads).

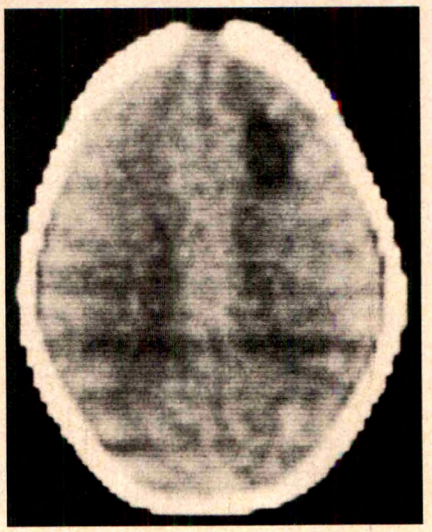

Fig 2.—Right porencephalic cyst after one month.

Fig 3.—Coronal section through porencephalic cyst. Membrane (arrowheads) separates cyst from lateral ventricle.

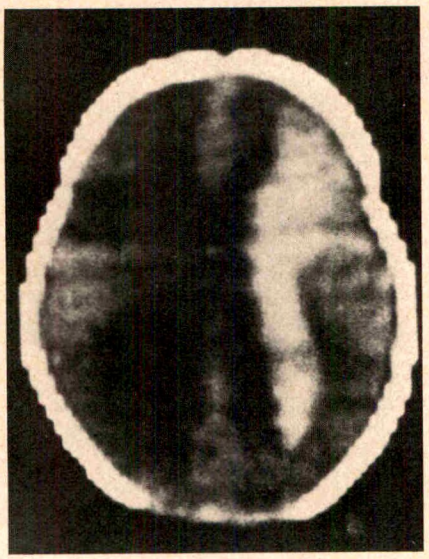

Fig 4.—Large hemorrhage in right lateral ventricle and frontal lobe.

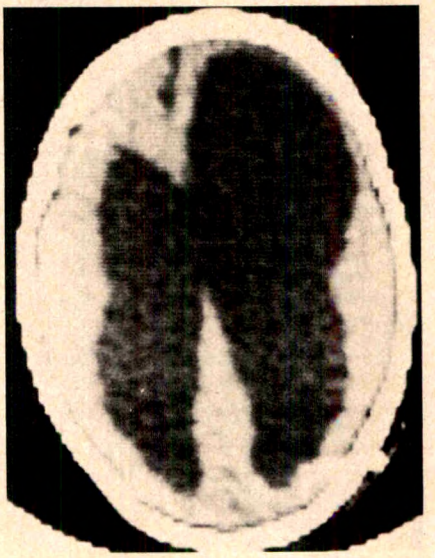

Fig 5.—Noticeable hydrocephalus and right frontal porencephalic cyst after one month.

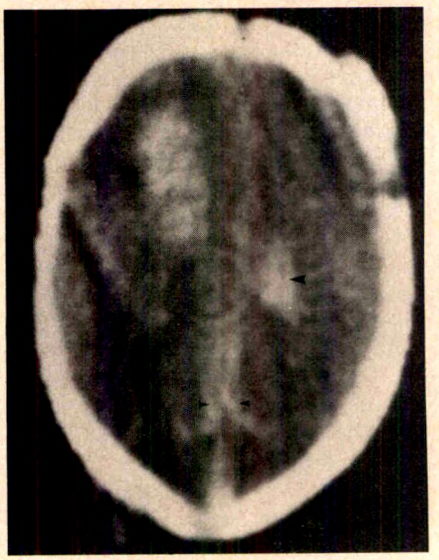

Fig 6.—Intraparenchymal blood can be seen in left frontal (large arrow) and right thalamic regions (small arrow). Blood can also be seen in intrahemispheric fissure posteriorly (smallest arrows).

hours of age, respiratory distress, hypothermia, bradycardia, and apnea had developed, and the child required assisted ventilation. The CSF contained 269,000/cu mm RBCs and a protein concentration of 1,520 mg/dL. Progressive ventricular dilation was not prevented by daily lumbar punctures or glycerin therapy, and she required a ventriculoperitoneal shunt at 5 months of age. Initial CT scan on postnatal day 13 showed a large intraventricular hemorrhage with a large right frontal, intraparenchymal hematoma (Fig 4). Subsequent CT scans demonstrated the development of right frontal porencephaly (Fig 5). At 5 months of age, she had severe psychomotor delay and a left hemiparesis with hyperreflexia and spasticity.

Case 4.—A male infant was born after a 30-week gestation. Birth weight was 1,380 g and the one- and five-minute Apgar scores were 7 and 9, respectively. In the first 24 hours of life, respiratory distress, hypotension, stupor, and a full anterior fontanelle developed. The CSF obtained on the first day of life had a hematocrit reading of 15%. A CT scan on the eighth postnatal day showed a large intraparenchymal hemorrhage in the left frontal area, a smaller hemorrhage in the right thalamus, and subarachnoid blood (Fig 6). Subsequent CT scans documented the resolution of the intraparenchymal hemorrhage and the appearance of a left frontal porencephalic cyst (Fig 7). At five months of age, he demonstrated moderate developmental delay and a subtle right hemiparesis, involving the face more than the extremities.

Case 5.—A female infant was the second born of twins after a 29-week gestation. She was delivered from a double footling breech presentation and Apgar scores at one and five minutes were 3 and 7, respectively. Birth weight was 1,240 g. Mild res-

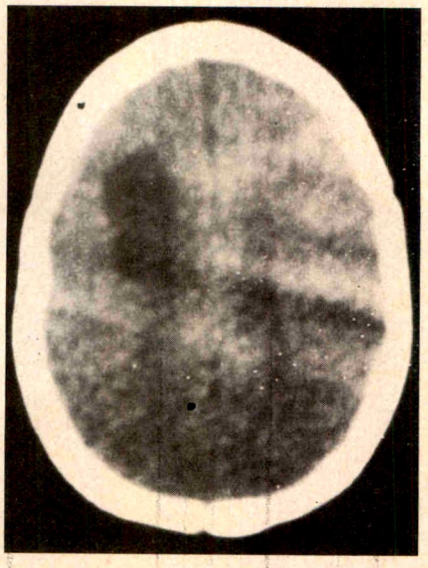

Fig 7.—Left frontal porencephaly at age 4 months.

piratory distress developed that required oxygen supplementation for 48 hours (maximum oxygen concentration, 40%). On the second day of life, the CSF contained 6,000/cu mm RBCs and a protein concentration of 900 mg/dL. A CT scan on the fifth day of life showed intraventricular hemorrhage, especially prominent on the right side, with extension into the right caudate nucleus. Subsequent CT scans documented the development of a small right frontal porencephalic cyst. At 1 month of age, results of physical examination were normal and without evidence of a focal deficit.

COMMENT

Yakovlev and Wadsworth[1] separated cystic cerebral lesions into schizencephaly and encephaloclastic cysts, ie, porencephaly. Schizencephaly appeared to be a true developmental defect of cerebral organogenesis, characterized by a restricted failure of formation of the cortical mantle. Heterotopic gray matter, polymicrogyria, and aberrant fibers were associated developmental abnormalities. These defects were generally bilateral and symmetric and communicated with the subarachnoid space. The typical encephaloclastic cyst, ie, porencephaly, is a fluid-filled defect within the cerebral parenchyma, the result of a destructive process. These cysts are usually unilateral and may communicate with the ventricular system. Most workers have attributed encephaloclastic porencephaly to occlusive arterial[2] or venous[3] disease.

Deonna et al[11] found unilateral cystic cavities that communicated with the ventricular system in four of ten infants with posthemorrhagic hydrocephalus. The diagnosis of intracranial hemorrhage in the neonatal period was made on the basis of the clinical syndrome and CSF findings. Unfortunately, the size and location of the intracranial blood was unknown in their patients, although each had an acute neurologic deterioration, suggesting that they had large hemorrhages.[10] The authors attributed the cystic lesions to ischemic injury to the periventricular white matter in combination with increased pressure within the ventricular system.

Our cases demonstrate that porencephaly may develop at the site of the intraparenchymal hemorrhage. In all four of our cases that have had demonstrable intracerebral hemorrhage by CT scan, the porencephalic cyst developed at the same site during the ensuing weeks. We believe that the pathogenesis of the porencephaly relates to the focal cerebral destruction by the hemorrhage rather than ischemia-induced periventricular encephalomalacia. Although increased intraventricular pressure is not necessary for the evolution of the porencephaly (case 4), such pressure may contribute to the development of the lesion. Thus, when intraventricular pressure is elevated and periventricular gray structures have been destroyed by the hemorrhage, herniation of the ventricular system into the cerebral mantle will be possible. These nuclear structures, eg, head of the caudate nucleus, tend to restrict dilation of the ventricles, as demonstrated by the usual occurrence in posthemorrhagic hydrocephalus of marked dilation of occipital horns and near normal size of the frontal horns of the lateral ventricles.[10]

Porencephaly subsequent to periventricular-intracerebral hemorrhage of the premature infant may be a relatively common lesion. Burstein et al[12] have described a similar evolution of intracerebral hemorrhage to porencephaly, although they did not include a clinical description. Our five infants were seen during an 18-month period and constituted two thirds of our surviving infants with large periventricular intracerebral-intraventricular hemorrhage. Moreover, the focal cerebral lesion contributes to the morbidity observed as a sequel to periventricular hemorrhage; indeed, focal motor deficit contralateral to the porencephaly was observed frequently in our cases early in infancy. Other clinical correlates, such as intellectual function, await longer-term follow-up.

This research was supported in part by the Allen P. and Josephine B. Green Foundation. Dr Volpe is a recipient of research career development award 1-K4-HD70608 from the National Institutes of Health.

Nonproprietary Name and Trademarks of Drug

Terbutaline sulfate—*Brethine, Bricanyl.*

References

1. Yakovlev PI, Wadsworth RC: Schizencephalies. *J Neuropathol Exp Neurol* 5:116-130, 1946.

2. Freeman JM, Gold AP: Porencephaly simulating subdural hematoma in childhood. *Am J Dis Child* 107:327-336, 1964.

3. Marburg O, Casamajo L: Phlebostasis and phlebothrombosis of the brain in the newborn and early childhood. *Arch Neurol Psychiatry* 52:170-188, 1947.

4. Challub EG, DeVivo DC, Siegal BA, et al: Coxackie A9 focal encephalitis associated with acute infantile hemiplegia and porencephaly. *Neurology* 27:574-579, 1977.

5. Navin JJ, Angevine JM: Congenital cytomegalic inclusion disease with porencephaly. *Neurology* 18:470-472, 1968.

6. Milhorat TH: *Pediatric Neurosurgery.* Philadelphia, FA Davis Co, 1978, pp 201-202.

7. Salmon JH: Puncture porencephaly. *Am J Dis Child* 114:72-79, 1967.

8. Papile L, Burstein J, Burstein R, et al: Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 grams. *J Pediatr* 92:529-534, 1978.

9. Ahmann PA, Lazarra A, Dykes FD, et al: Intraventricular hemorrhage: Incidence and outcome, abstracted. *Ann Neurol* 4:186, 1978.

10. Volpe JJ: Neonatal intracranial hemorrhage: Pathophysiology, neuropathology and clinical features. *Clin Perinatol* 34:77-102, 1977.

11. Deonna T, Payot M, Probst A, et al: Neonatal intracranial hemorrhage in preterm infants. *Pediatrics* 56:1056-1064, 1975.

12. Burstein J, Papile L, Burstein R: Intraventricular hemorrhage and hydrocephalus in premature newborns: A prospective study with CT. *Am J Roentgenol* 134:631-635, 1979.

The Effect of Circumcision on Transcutaneous Po_2 in Term Infants

David J. Rawlings, MD; Patricia Anne Miller; Rolf R. Engel, MD

• To assess the effect of pain on Pao_2 in newborns, transcutaneous Po_2 ($tcPo_2$) was monitored in ten healthy male infants undergoing circumcision. The $tcPo_2$ was seen to decrease to a lower level with pain and to remain low with continuing pain. After the circumcision, the $tcPo_2$ increased to levels equal to or exceeding those of the preoperative baseline period. Close concordance of $tcPo_2$ above and below the waist demonstrated no right-to-left shunting through the ductus arteriosus.

(*Am J Dis Child* 134:676-678, 1980)

Investigators[1-5] who have correlated Pao_2 with transcutaneous Po_2 ($tcPo_2$) have obtained blood samples from indwelling arterial lines because of concern that the pain of an arterial puncture may disturb oxygenation. To further define the effect of pain on $tcPo_2$, normal male infants were monitored during circumcision. Simultaneous monitoring of the $tcPo_2$ over the right upper side of the chest and left lower part of the abdomen enabled us to evaluate the possibility of right-to-left shunting through the ductus arteriosus during the procedure of circumcision.

SUBJECTS AND METHODS

Ten healthy male infants were circumcised at 48 to 72 hours of age after obtaining informed consent from the parents. All were born at term with one-minute Apgar scores greater than 7 and a mean birth weight of 3,350 g. Neither heart murmurs nor abnormal femoral artery pulses were detected immediately prior to circumcision.

The procedure consisted of the following: about five minutes of cleaning the penis with povidone-iodine (Betadine) solution; adhesion lysis between glans and foreskin; dorsal foreskin clamping with forceps for

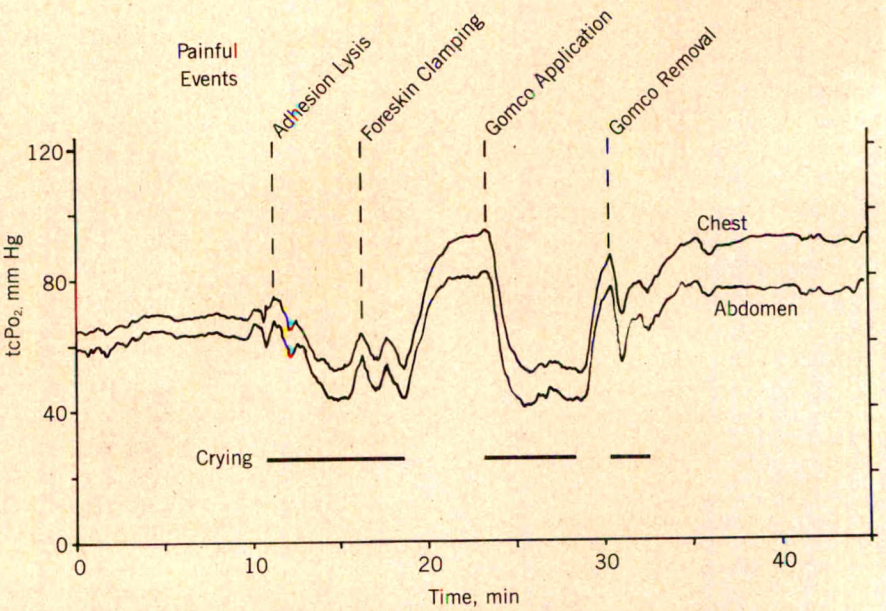

Fig 1.—Continuous recording of transcutaneous Po_2 ($tcPo_2$) on chest and abdomen during circumcision. Abdominal tracing was shifted down 8 mm Hg for clarity.

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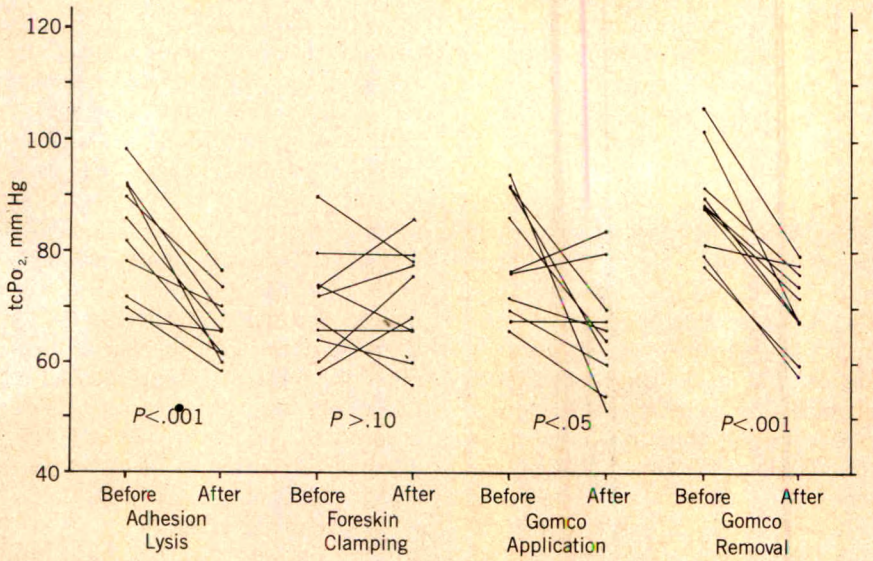

Fig 2.—Chest transcutaneous Po_2 ($tcPo_2$) immediately before and maximum change within two minutes after onset of painful events for ten infants.

Heart Rate, Respiratory Rate, and $tcPo_2$* at Circumcision

	Operative Periods		
	Before	During	After
Heart rate, beats/min			
Mean	122	165*	138†
SD	26	21	28
Range	99-174	137-197	98-180
Respiratory rate, breaths/min			
Mean	43	50†	53†
SD	12	11	12
Range	22-64	39-77	40-79
$tcPo_2$, mm Hg*			
Mean	75	82	85†
SD	8	17	12
Range	62-88	66-129	65-106

*$tcPo_2$ indicates transcutaneous Po_2, which was measured below right clavicle.
†Significantly ($P < .05$) greater than preoperative value.

two to four minutes, followed by forceps removal and division of the crushed skin. A bloodless circumcision clamp (Gomco) was applied for five minutes before the foreskin was amputated. To discern the effect for each of the four painful manipulations, the interval from adhesion lysis to circumcision clamp removal was extended to 20 minutes.

Throughout the study, a radiant overhead warmer was used to maintain the abdominal skin temperature at 36.0 °C. A nipple was offered for nonnutritive sucking. The period of continuous monitoring included at least 20 minutes before and after the circumcision. Transcutaneous oxygen electrodes (TCM1 Radiometer) were affixed below the right clavicle and to the left of the umbilicus. Both electrodes were thermally insulated with expanded rigid polystyrene plastic caps so that the electrode heat consumption served as an indirect measure of local blood flow.[6] Respiratory and heart rates were monitored with vital signs modules. All parameters were recorded continuously on a potentiometric recorder. The $tcPo_2$ electrodes were interchanged at the end of the monitoring periods to help separate instrumentation from physiologic differences. Average values were obtained from planimetry of the tracings.[7] Statistical comparisons used two-tailed paired t testing.

RESULTS

Each of the studies demonstrated close concordance between the $tcPo_2$ tracings from the chest and abdomen (Fig 1). None of the infants showed a significant difference between chest and abdominal $tcPo_2$ during quiet or crying intervals. Both $tcPo_2$ tracings decreased with pain and remained at a lower level until crying ceased. During brief respites from crying, the $tcPo_2$ rebounded partially, and with longer quiet periods, the preoperative $tcPo_2$ was often exceeded.

The change in $tcPo_2$ after the four painful procedures involved in circumcision was plotted for each of the ten subjects (Fig 2). There was a significant decrease in $tcPo_2$ for all 40 events considered together ($P < .001$) and for three of the four individual categories. The average decrease in the $tcPo_2$ was 15 mm Hg for adhesion lysis, less than 1 mm Hg for foreskin clamping, 13 mm Hg for circumcision clamp application, and 19 mm Hg for circumcision clamp removal. The negligible response to foreskin clamping probably reflects the absence of a quiet interval before this event in contrast to adhesion lysis and circumcision clamp removal, both of which followed manipulation-free intervals of five or more minutes, and circumcision clamp application, which was preceded by variable freedom from stimulation. The average postevent $tcPo_2$ for each of the four manipulations was not significantly different than that for any of the other three.

The average $tcPo_2$ was increased during the postoperative period. ($P < .05$, Table). Electrode heat consumption remained constant throughout the study, with no difference between chest and abdominal electrodes. The average heart and respiratory rates were higher during the intraoperative and postoperative periods as compared with the preoperative interval ($P < .05$, Table).

COMMENT

Circumcision in neonates has been shown to affect adrenal cortical func-

tion,[8] immediate postoperative behavior,[9-11] and possibly long-term behavior.[12] The present study demonstrates that circumcision also affects the heart rate, respiratory rate, and $tcPo_2$ both during and immediately after the procedure. The observed decrease in $tcPo_2$ with pain might result from momentary decreases in alveolar ventilation during crying. Right-to-left shunting at the atrial level, with crying, as shown by Lind et al[13] during the first 2 weeks of life, is also a possible explanation. The close concordance of chest and abdominal $tcPo_2$ indicates that despite vigorous crying, right-to-left shunting through the ductus arteriosus did not occur in our sample of 2- to 3-day-old, term male infants. The absence of hypoxic symptoms in this group of term infants is in accord with the prediction that healthy infants should not be compromised by a transient decrease of 20 mm Hg in $tcPo_2$.

The 10 mm Hg increase in mean $tcPo_2$ after the circumcision could reflect increased minute ventilation in lungs fully expanded from recent crying. Although Martin et al[5] have also observed mean $tcPo_2$ levels less than 80 mm Hg in healthy infants, it is possible that an allowance should be made for the thicker skin of term infants since the electrode temperature of 44 °C and the warm-up period of 20 minutes were based on correlation (r = .95) between $tcPo_2$ and Pao_2 in premature infants.

The response to pain by each individual infant was surprisingly consistent. That is, some infants had abrupt decreases in $tcPo_2$ and increases in heart and respiratory rates with each of the painful stimuli while other infants repeatedly had attenuated responses. These individual variations in the response to pain underline the limited reliability of arterial punctures for assessment of resting Pao_2. Since the $tcPo_2$ often exceeded baseline values after crying ceased, there is also the possibility that delay in drawing an arterial blood sample could result in obtaining a Pao_2 that is greater than the baseline.

References

1. Krauss AN, Waldman S, Frayer WW, et al: Noninvasive estimation of arterial oxygen in newborn infants. *J Pediatr* 93:275-278, 1978.
2. Friis-Hansen B, Marstand-Christiansen P, Vesterager P: Transcutaneous measurement of arterial blood oxygen tension with a new electrode. *Scand J Clin Lab Invest* 37(suppl 146):31-36, 1977.
3. Okken A, Rubin IL, Martin RJ: Intermittent bag ventilation of preterm infants on continuous positive airway pressure: The effect on transcutaneous Po_2. *J Pediatr* 93:279-282, 1978.
4. Huch R, Huch A, Albani M, et al: Transcutaneous Po_2 monitoring in routine management of infants and children with cardiorespiratory problems. *Pediatrics* 57:681-690, 1976.
5. Martin RJ, Okken A, Rubin D: Arterial oxygen tension during active and quiet sleep in the normal neonate. *J Pediatr* 94:271-274, 1979.
6. Peabody JL, Willis MM, Gregory GA, et al: Reliability of skin (tc) Po_2 electrode heating power as a continuous noninvasive monitor of mean arterial pressure in sick newborns. *Birth Defects* 15:127-133, 1979.
7. Yang SS, Bentivoglio LG, Maranhao V, et al: *From Cardiac Catheterization to Hemodynamic Parameters*, ed 2. Philadelphia, FA Davis Co, 1978, pp 51-54.
8. Talbert LM, Kraybill EN, Potter HD: Adrenal cortical response to circumcision in the neonate. *Obstet Gynecol* 48:208-210, 1976.
9. Anders TF, Chalemain RJ: The effects of circumcision on sleep-wake states in human neonates. *Psychosom Med* 36:174-179, 1974.
10. Emde RN, Harmon RJ, Metcalf D, et al: Stress and neonatal sleep. *Psychosom Med* 33:491-497, 1971.
11. Marshall PE, Stratton WC, Moore JA, et al: Circumcision: Effects upon newborn behavior: A controlled, blind, observational study. *Pediatr Res* 12:334, 1979.
12. Richards MP, Bernal JF, Brackbill Y: Early behavioral differences: Gender or circumcision? *Dev Psychobiol* 9:89-95, 1976.
13. Lind J, Stern L, Wegelius C: *Human Foetal and Neonatal Circulation*. Springfield, Ill, Charles C Thomas Publisher, 1964.

Aerobic and Anaerobic Bacteriology of Pilonidal Cyst Abscess in Children

Itzhak Brook, MD, MS; Kathryn D. Anderson, MD; Guido Controni, MS; William J. Rodriguez, MD, PhD

• **Aspirates of pus from pilonidal abscesses in 25 children were studied for aerobic and anaerobic bacteria. A total of 76 isolates (63 anaerobic and 13 aerobic) were recovered from the patients, accounting for 2.52 anaerobes and 0.52 aerobes per specimen. Anaerobic organisms were recovered from all the specimens, and in eight cases (32%) they were mixed with aerobic organisms. The predominant anaerobic organisms were *Bacteroides* sp (36 isolates, including ten *B fragilis* group and ten *B melaninogenicus* group), Gram-positive anaerobic cocci (16), *Fusobacterium* sp (five), and *Clostridium* sp (four). The predominant aerobic organisms were *Escherichia coli* (four) and group D streptococci, α-hemolytic streptococci, and *Proteus* sp (two of each). We believe this study is the first to demonstrate the mixed anaerobic and aerobic bacteriology of pilonidal cyst abscesses in children.**

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Pilonidal sinus is commonly encountered in pediatric patients, especially in the adolescent age group. Pilonidal sinus infection is often protracted, causes local irritation, and may in rare cases lead to serious complications, such as bacteremia or meningitis. To our knowledge, the bacteriologic features of infected pilonidal cyst in children have never been studied with anaerobic and aerobic bacteriology techniques. Most of the data in the literature are derived from studies done in adults.[1] This study was designed to determine the aerobic and anaerobic bacteriologic features of pilonidal cyst abscess in pediatric patients.

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SUBJECTS AND METHODS

The 25 children included in the study were treated at Children's Hospital National Medical Center, Washington, DC, for a pilonidal cyst abscess that required surgical drainage. Mean age of the patients was 7 years and 3 months (range, 10 months to 14 years). Thirteen were girls. Eight of the patients received antimicrobial therapy prior to sample collection.

Cultures were obtained by direct needle aspiration of the purulent content into a syringe that was immediately sealed, or by a swab that was dipped in the pus and introduced into anaerobic transport media. The specimens were transported to the bacteriology laboratory and inoculated within ten to 30 minutes after collection.

Sheep blood (5%), chocolate, and MacConkey's agar plates were inoculated for the isolation of aerobic organisms. The plates were incubated at 37 °C aerobically (MacConkey's) and under 5% CO_2 (blood and chocolate), and examined at 24 and 48 hours. For the isolation of anaerobes, the specimens were plated onto prereduced vitamin K_1-enriched *Brucella* blood agar, an anaerobic blood agar plate containing kanamycin sulfate (75 μg/mL) and vancomycin hydrochloride (7.5 μg/mL), an anaerobic blood plate containing phenylethyl alcohol, and an enriched thioglycolate broth.[2] These media were incubated inside anaerobic jars at 37 °C, and examined at 48 and 96 hours. The thioglycolate broth was incubated for 14 days. Anaerobes were identified by techniques previously described.[2] Aerobic bacteria were identified by means of conventional methods.[3] β-Lactamase activity was determined on all isolates with use of the chromogenic cephalosporin analog 83/312 methodology.[4]

RESULTS

All 25 specimens yielded bacterial growth that included anaerobic organisms. Mixed aerobic and anaerobic bacteria were present in eight patients (32%), and anaerobic bacteria only were present in 17 of the patients (68%). A total of 76 anaerobic and aerobic isolates were recovered from the patients, accounting for 3.04 isolates per specimen (2.52 anaerobes and 0.52 aerobes per specimen) (Table).

A total of 63 anaerobic isolates were recovered from the patients. The predominant anaerobes recovered, in descending order of frequency, were as follows: *Bacteroides* sp (36 instances, including ten *B fragilis* group and ten

Bacterial Isolates From 25 Pilonidal Cyst Abscesses in Children	
Isolates	**No.**
Aerobic and facultative	
Gram-positive cocci	
α-hemolytic streptococci	2
Group D streptococci	2
Nonhemolytic streptococci	1
Staphylococcus aureus	1
Gram-negative bacilli	
Proteus sp	2
Escherichia coli	4
Klebsiella pneumoniae	1
Total	**13**
Anaerobic	
Gram-positive cocci	
Peptococcus sp	11
Peptostreptococcus sp	5
Gram-negative cocci	
Veillonella sp	1
Gram-positive bacilli	
Clostridium perfringens	2
Clostridium sp	2
Propionibacterium acnes	1
Gram-negative bacilli	
Fusobacterium sp	3
F nucleatum	2
Bacteroides sp	9
B melaninogenicus	10
B rum ssp *brevis*	2
B fragilis) B.	5
B vulgatus) *fragilis*	1
B distasonis) group	2
B thetaiotaomicron	2
B ovatus	2
B corrodens	3
Total	**63**

B melaninogenicus group), anaerobic Gram-positive cocci (16), *Fusobacterium* sp (five), and *Clostridium* sp (four).

A total of 13 aerobic isolates were recovered. The predominant aerobic isolates were *Escherichia coli* (four), and group D streptococci, *Proteus* sp, and α-hemolytic streptococci (two of each). There was no consistent pattern of combination; however, in every instance in which *Bacteroides* sp was isolated, Gram-positive anaerobic cocci were present.

β-Lactamase production was detected in 12 isolates. These included all isolates of *B fragilis* (10) and *Staphylococcus aureus* (one) and two of the ten isolates of *B melaninogenicus*.

COMMENT

This study discusses our experience in the isolation of aerobic and anaerobic bacteria from pilonidal cyst abscesses in children. To the best of our knowledge, no such data relating to pediatric patients have been published.

Recently, Finegold[1] summarized 13 publications dealing with the bacteriologic characteristics of infected pilonidal cyst in adults. The most frequent isolates reported in those studies were various *Bacteroides* sp, including *B fragilis*, anaerobic Gram-positive cocci, and *Clostridium* sp. A recent report[6] presented the bacteriologic features of pilonidal cyst abscess in 11 adults. Anaerobic organisms, such as *Bacteroides* sp and Gram-positive anaerobic cocci, were the predominant isolates. Gram-negative enteric bacteria and *S aureus* were not present.

Our bacteriological study of pilonidal cyst abscess in children demonstrated that anaerobic organisms, the predominant isolates in these infections, outnumber aerobes in a ratio of 5 to 1. In contrast to other investigators,[5,6] we have been able to retrieve Gram-negative aerobic bacilli in five instances. Like other investigators, we did not find *S aureus* to be a predominant isolate in this type of infection.

The isolation of anaerobic bacteria mixed with aerobic and facultative organisms at that site is not surprising since anaerobes are the predominant organisms in the gastrointestinal tract where they outnumber aerobes in the ratio of 1,000:1.[7] Since anaerobic bacteria are frequently associated with pilonidal abscess in pediatric patients, the physicians should consider their presence if antimicrobial therapy is used. Gram staining of aspirated pus and appropriate aerobic and anaerobic techniques can help the physician select proper therapy. Since some of the anaerobes are resistant to penicillin, therapy should also include appropriate coverage of those organisms. Surgical drainage is still the therapy of choice. However, the presence of penicillin-resistant anaerobic bacteria, such as *B fragilis*[8] and some strains of *B melaninogenicus*,[8,9] may warrant the administration of appropriate antimicrobial agents, such as clindamycin, chloramphenicol, cefoxitin, carbenicillin disodium, ticarcillin disodium, or metronidazole.

Leslie Calhoun, MS, Linda Harteker, MS, and the staff of the clinical microbiology laboratory at the Children's Hospital National Medical Center cooperated in this study.

Nonproprietary Names and Trademarks of Drugs

Cefoxitin—*Mefoxin.*
Clindamycin—*Cleocin.*
Metronidazole—*Flagyl.*
Ticarcillin disodium—*Ticar.*
Vancomycin hydrochloride—*Vancocin Hydrochloride.*

References

1. Finegold SM: *Anaerobic Bacteria in Human Disease.* New York, Academic Press Inc, 1977, p 389.
2. Sutter VL, Vargo VL, Finegold SM: *Wadsworth Anaerobic Bacteriology Manual,* ed 2. Los Angeles, UCLA Extension Division, 1975.
3. Lennette EH, Spaulding EH, Traunt R Jr: *Manual of Clinical Microbiology,* ed 2. Washington, DC, American Society for Microbiology, 1974.
4. O'Callagham CH, Morris A, Kirby SM, et al: Novel method for detection of β-lactamase by using a chromogenic cephalosporin substrate. *Antimicrob Agents Chemother* 1:283-288, 1972.
5. Marrie TJ, Aylwarad D, Kerr E, et al: Bacteriology of pilonidal cyst abscesses. *J Clin Pathol* 31:909, 1978.
6. Meislin HW, Lerner SA, Graves MH, et al: Cutaneous abscesses: Anaerobic and aerobic bacteriology and outpatient management. *Ann Int Med* 87:145-149, 1977.
7. Gorbach SL: Intestinal microflora. *Gastroenterology* 60:1110-1129, 1971.
8. Sutter VL, Finegold SM: Susceptibility of anaerobic bacteria to 23 antimicrobial agents. *Antimicrob Agents Chemother* 10:736-752, 1976.
9. Murray PR, Rosenblatt JE: Penicillin resistant and penicillinase production in clinical isolates of *Bacteroides melaninogenicus. Antimicrob Agents Chemother* 11:605-608, 1977.

Acute Glomerulonephritis and Streptococcal Skin Lesions in Eskimo Children

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• Poststreptococcal acute glomerulonephritis often follows impetigo and can occur in epidemics. From 1975 through 1977, an epidemic of poststreptococcal acute glomerulonephritis occurred in Alaska. Fifty children required hospitalization, while 25 less seriously ill children were treated as outpatients. Sixty-seven percent of these 75 children had direct evidence of recent skin infections. Serotypes 49-14 and NT-14 were the most common streptococcal isolates. In villages in the epidemic area, approximately 15% of children had impetigo and more than 60% of lesions cultured were positive for group A streptococci. Impetigo rates in the epidemic area were similar to those found in nonepidemic areas. However, the introduction of the nephritogenic streptococcal serotypes not recently present in this population apparently led to the development of the epidemic.

(*Am J Dis Child* 134:681-685, 1980)

Impetigo usually occurs when mild skin trauma becomes secondarily infected with group A streptococci.[1] Although suppurative complications from impetigo are rare,[2] the nonsuppurative complication of acute glomerulonephritis may frequently occur following infections with certain serotypes of streptococci.[3] Classically, impetigo has been thought to be a disease of warm or temperate climates,[1,2,4] although it has been reported in arctic regions.[5] Beginning in 1975, an epidemic of impetigo-related poststreptococcal acute glomerulonephritis occurred in Eskimo children living in southwestern Alaska, and had considerable impact on the health care facilities and families living in that region.

Approximately 15,000 Yupik-speaking Eskimos live in 53 villages located on the delta of the Yukon and Kuskokwim rivers in southwestern Alaska. Primary health care in each village is provided by trained community health aides, and patients with serious illness are referred to the 42-bed Public Health Service Alaska Native Hospital located in the town of Bethel, the transportation center of the region.

A mail-in streptococcal culture program that included grouping and typing of isolates had been introduced in the area in 1971 as one part of a program to reduce the incidence of acute rheumatic fever. The presence of this program in the region prior to and during the epidemic of acute glomerulonephritis provided a unique opportunity to describe the epidemic features of streptococcal disease in remote communities in relation to the occurrence of acute glomerulonephritis. We describe the epidemic and its clinical features and relate the epidemic to the distribution of strepto-

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coccal disease and pyoderma in Eskimo children.

METHODS

Sources of Data

The medical record system of the Alaska Area Native Health Service was used to identify cases of poststreptococcal glomerulonephritis during the pre-epidemic period July 1971 through September 1975. Charts were reviewed and pre-epidemic rates of poststreptococcal glomerulonephritis were established. The following were determined in order to compare the occurrence of impetigo in the epidemic area served by the Bethel hospital with nonepidemic areas. First, the prevalence of impetigo among children aged 6 months through 14 years was determined in 13 Eskimo villages through active screening during physical examinations conducted in the field. Of the 13 villages, six were in the Bethel region, while seven were in the Bristol Bay region, an area considered nonepidemic. In addition, the frequency of outpatient visits for impetigo at the Alaska Native Health Center in Fairbanks, 854 km northeast of the epidemic area, were compared with those for the Bethel facility.

Clinical and Laboratory Examinations

Children who came to the clinic and were suspected of having poststreptococcal acute glomerulonephritis during the epidemic period were evaluated by measurement of blood pressure, chest roentgenogram, and serial measurements of weight. Routine clinical laboratory determinations included urinalysis, complete blood cell count, and measurements of serum electrolytes, BUN, creatinine, ESR, quantitative urine protein, and creatinine clearance. The C3 level was determined by radial immunodiffusion. Antistreptolysin O (ASO) determinations were performed routinely on hospital admissions. Sera from patients were stored at −70 °C, and at a later date ASO and antideoxyribonuclease B (ADN-B) determinations were performed on these specimens with use of microtitration techniques[6,7] and a 60, 85 dilution scheme. For Alaskan Eskimos, the upper limits of normal for ASO and ADN-B were determined from an age-stratified group of 80 children. These children, participants in the streptococcal surveillance program, had no positive cultures for streptococci in spite of repeated testing during a one-year period and also had no change (<0.3 log) in antibody titer for this same period. The calculated upper limit of normal[8] for ASO (ages 2 to 14 years) was 170; for ADN-B (ages 2 to 14 years), it was 480. The normal upper limits for both ASO and ADN-B resemble those reported for uninfected children in Alabama by Dillon and Avery.[9]

Throat cultures were obtained, and impetiginous lesions were cultured after the scab was removed. The cotton swabs were placed in silica gel[10] and mailed to the Anchorage laboratory, where they were incubated at 37 °C for four to six hours in Todd-Hewitt broth. An inoculum of the broth was used to prepare sheep blood-agar pourplates, which were then incubated at 37 °C for 18 to 20 hours. *Streptococcus*-like colonies were subcultured and grouped by the Lancefield method.[11] Group A extracts were typed by T-agglutination and M-precipitin tests[12] with antiserum provided by Bureau of Laboratories, Center for Disease Control, Atlanta.

Definitions

A case of poststreptococcal acute glomerulonephritis was defined as a patient with recent onset of hematuria plus at least two of the following findings: hypertension, edema, signs of vascular overload on chest roentgenogram (cardiomegaly, effusions, increased pulmonary vascularity), hypocomplementemia, or evidence of recent streptococcal infection (positive culture, history of impetigo or pharyngitis, or elevated ASO titer).

Table 1.—Laboratory Findings During the Clinical Illness

Determination	Outpatient No.	Outpatient %	Hospitalized No.	Hospitalized %
Hematuria (microscopic)	25/25	100	50/50	100
Hematuria (chemical)	22/25	88	48/50	96
Cylinduria				
RBCs	6/25	24	19/50	38
Other	3/25	12	18/50	36
Pyuria				
<5 WBC/high-power field	20/25	80	27/50	54
5-10 WBCs/high-power field	3/25	12	7/50	14
>10 WBCs/high-power field	2/25	8	16/50	32
Proteinuria (≥1+ dipstick)	12/25	48	47/50	94
24-hr urine protein				
<100 mg	...	...	1/24	4
100-599 mg	...	...	14/24	58
600-1,000 mg	...	...	5/24	21
>1 g	...	...	4/24	17
BUN				
<20 mg/dL	13/23	57	17/48	35
20-40 mg/dL	3/23	13	26/48	54
>40 mg/dL	1/23	4	5/48	10
C3				
<40 mg/dL	13/22	59	33/45	73
40-85 mg/dL	8/22	36	9/45	20
86-100 mg/dL	1/22	5	0/45	0
>100 mg/dL	0/22	0	3/45	7

RESULTS

Acute Glomerulonephritis

Epidemiologic Findings.—Seventy-five children in 50% of the villages in the Bethel region fulfilled the case definition for poststreptococcal glomerulonephritis from October 1975 through December 1977. Only seven cases were identified through chart review for the preceding years. Fifty patients (67%) were hospitalized because of symptoms of volume overload, and 25 were treated as outpatients. All patients were children under 15 years of age. The mean age was 6 years 10 months (range, 19 months to 14 years). Both sexes were equally affected.

Clinical and Laboratory Findings.—Hypertension was present in 68% of the cases (94% of hospitalized patients and 16% of outpatients). Among inpatients, the average weight loss from diuresis was 7.7% of the initial body weight (range, 3% to 15%). The mean duration of hospitalization was seven days, and patients were discharged when there was no further evidence of hypertension and there were indications that diuresis had begun. Many

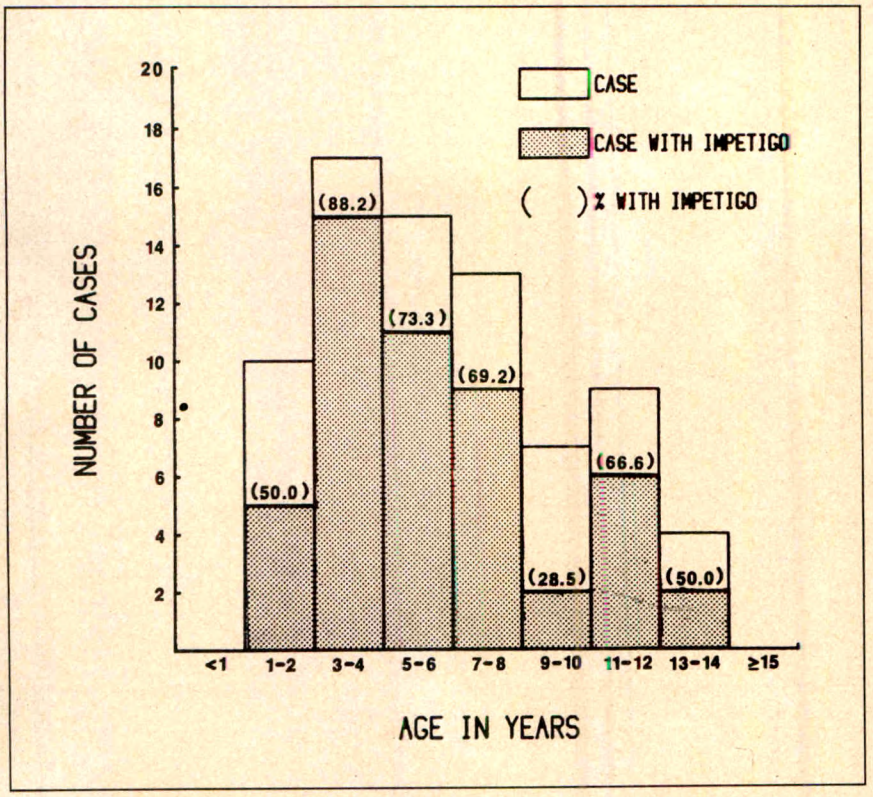


Fig 1.—Age-specific frequency of impetigo in relation to age distribution of Eskimo children with poststreptococcal acute glomerulonephritis: number of cases of acute glomerulonephritis (open portion); number of cases of impetigo (shaded portion); age-specific frequency of impetigo (parenthetical numbers).

children were found to have abnormalities of urine sediment and serum (Table 1). The mean creatinine clearance for 24 inpatients was 55.5 mL/min/1.73 sq m (range, 13 to 111 mL/min/1.73 sq m). Chest roentgenograms showed abnormal findings in 34 of 43 inpatients and in nine of 19 outpatients. Cardiomegaly, the most frequent abnormality documented by roentgenogram, occurred in 72% of those studied. In those with cardiomegaly, other abnormalities also were found, including increased pulmonary vascularity (19%) and pleural effusions (16%). Fifteen percent of all roentgenograms showed evidence of lobar consolidation, and in all but one case, this finding occurred in children without signs of volume overload.

Streptococcal Isolates and Serologic Findings.—Of the 75 children with acute glomerulonephritis, 50 (67%) had evidence of impetigo on physical examination (32 children) or by history (18 children), and the age group most affected in the epidemic (3 to 4 years) was the age group most likely to have skin lesions (Fig 1). Of the 32 children with evidence of impetigo on physical examination, 21 (65%) had skin lesions positive for group A streptococcal organisms, and while impetigo cultures from the remaining 11 children were negative, one had a positive throat culture. Of the 18 children with a history of impetigo (but who were free of skin lesions at the time of examination), eight had throat cultures positive for group A streptococcal organisms. Of the 25 children without evidence of impetigo either by history or by examination, eight had a positive throat culture. Typing of the available group A streptococcal isolates from all sites revealed that 25 were non-M-typable T-type 14 (NT-14), six were M-type 49 T-type 14 (49-14), two were NT-B3264, and one was NT-3/13/B3264. Of the remaining 17 children with neither evidence of impetigo nor a positive throat culture, all but one had serologic evidence of recent streptococcal infection.

Both ASO and ADN-B titers were measured on 35 of the children with acute glomerulonephritis. The geometric mean for the ASO titers was 196 (range, <60 to 960) and 36% were above the upper limit of normal. The geometric mean for the ADN-B titers was 653 (range, 240 to 3,840) and 58% were abnormal. There were no differences between the titers of inpatients and outpatients. Overall, 69% of the ill children had at least one serologic test result that was abnormal.

Streptococcal Skin Infections

Epidemiologic Features.—From 1974 through 1977, impetigo accounted for an average of 0.8% of the total outpatient visits at the Bethel hospital. At the Alaska Native Health Center in Fairbanks, 854 km northeast of the epidemic area, impetigo accounted for 1.4% of the outpatient visits during this same time period. The yearly rates in both facilities did not vary significantly during the four-year period. In both areas, seasonal variation in outpatient visits for impetigo occurred, but the variation was similar in both facilities (Fig 2).

When 593 children were surveyed during January 1976 in six Bethel area villages initially involved in the epidemic, 79 (13%) had impetigo. These same children were studied when the epidemic had ended in their villages (September 1976), and of 434 examined, 63 (15%) had impetigo. Of the 535 Bristol Bay area children not involved in the epidemic when surveyed during August 1977, a total of 104 (19%) had skin infections.

Preschoolers were the age group most often seen with impetigo at the hospital outpatient department; however, in the village populations surveyed, impetigo was not limited to children in any one age group (Table 2).

Streptococcal Isolates.—Cultures for the isolation of streptococci were obtained from impetiginous lesions of children in the villages surveyed in the area around Bethel. Of 63 children cultured in January 1976, 80% were positive for group A streptococci, and during September 1976, when 55 children were cultured, 52% had positive cultures. From 1976 through 1977,

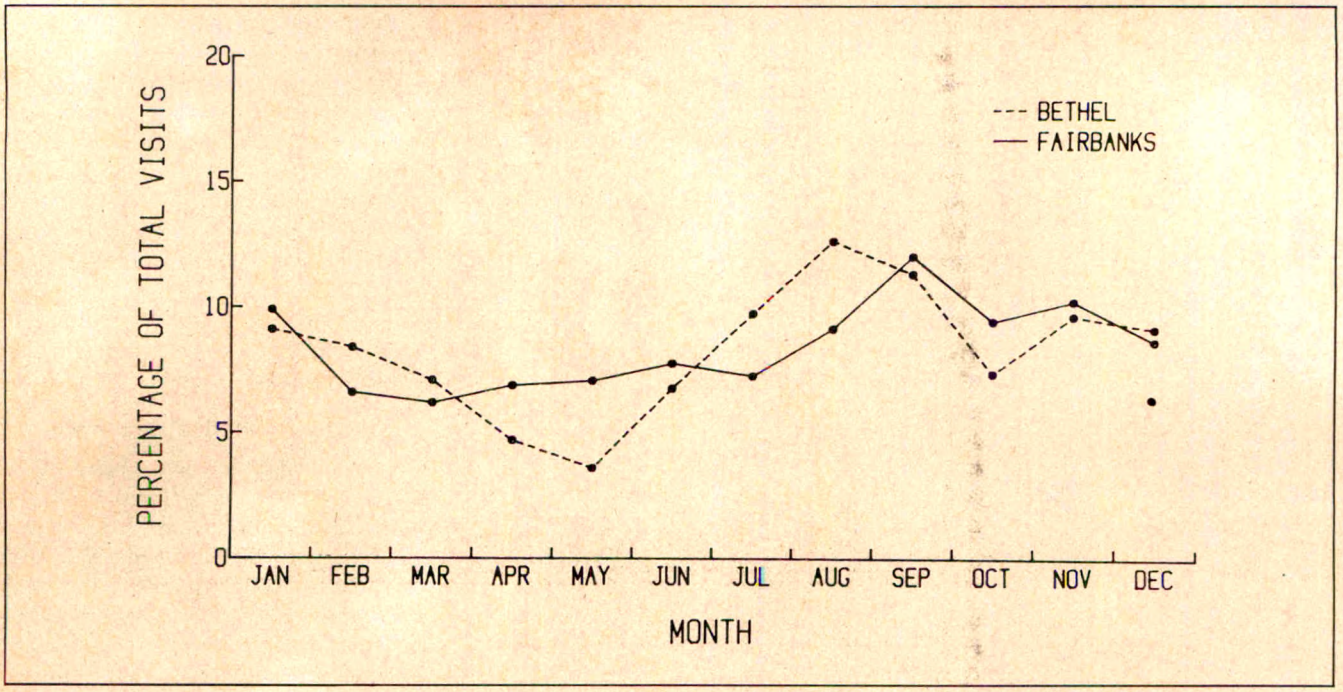


Fig 2.—Distribution of visits to outpatient clinics in Bethel and Fairbanks, arranged by month of year and averaged during four years (1974 to 1977).

Table 2.—Age Distribution of Impetigo in Eskimo Children

Source of Data*	Frequency of Impetigo, % (Age Groups, yr) <1	1-4	5-9	10-14
Outpatient visits, 1974-1977 (N = 1,562)	10.2	56.1	22.0	11.5
Village surveys, 1976, 1977				
Bethel villages, epidemic (N = 79)	5.7	28.8	28.8	30.7
Bethel villages, postepidemic (N = 63)	3.2	32.2	43.5	22.5
Bristol Bay villages, nonepidemic (N = 104)	2.1	25.5	34.0	38.3

*N indicates number of children with impetigo.

Table 3.—Frequency of Streptococcal Serotypes Isolated From Impetigo, Bethel Area, 1976 to 1977

Serotyping T-pattern	M-type	Village Surveys, %* January 1976 (N = 47)	September 1976 (N = 29)	Mail-in Cultures (%) 1976-1977 (N = 744)
14	NT†	51	50	32
14	49	9	3	30
3/13/B3264	NT	13	0	22
3/13/B3264	41•	11	27	<1
28	NT	6	0	10
29	NT	0	20	0
Other‡		11	0	5

*N indicates number of group A isolates typed.
†NT indicates nontypable.
‡Other serotypes included were NT 6/23, NT 13, NT 12, NT 6, NT 5/27/44, 1-1, 4-4.

1,246 cultures of impetiginous lesions from children in Bethel and surrounding villages were submitted through the mail-in streptococcal surveillance program, and 69% were positive for group A streptococci. The nephritogenic strain, T-type 14, often in association with M-type 49, was the most common serotype identified (Table 3). In the five years prior to September 1975, this serotype had not been found in thousands of cultures (mostly throat cultures) collected throughout Alaska.

COMMENT

Epidemic acute glomerulonephritis in association with impetigo has been reported from both tropical[4] and temperate regions.[3,13,14] Although impetigo has previously been reported among children living in the Arctic,[5] there have been no other published reports of the occurrence of epidemic glomerulonephritis in the Arctic. Children with glomerulonephritis seen at the Bethel hospital during this epidemic had a clinical picture similar to that reported during epidemics occurring in other locales,[4,13,14] and signs of volume overload predominated in the children with the most serious illness.

Evidence of an antecedent streptococcal infection was documented in all but one child. The skin was the predominant site of infection, and ADN-B titers were elevated more often than ASO titers.

The rate of impetigo, its seasonal variation, and the age distribution of those affected are similar in Alaska to findings reported for temperate regions,[15,16] even though the climates are different. Eskimo children have a considerable amount of streptococcal skin colonization and skin trauma from insect bites, scabies, and frostbite, all of which may predispose them to impetigo. Other studies of children with poststreptococcal acute glomerulonephritis have shown that this disease is strongly associated with infection of the skin.[4,13,17] This was our finding clinically and we were also able to demonstrate through village surveys that the age-specific rates of impetigo in children with acute glomerulonephritis were higher than the age-specific prevalence of impetigo present in the general population. However, there was no evidence that impetigo rates themselves changed markedly before or after the epidemic or that rates differed in regions with or without epidemic acute glomerulonephritis. As the epidemic progressed, fewer of the children with acute glomerulonephritis had impetiginous lesions that were positive when cultured for streptococcal organisms. This decrease in isolates may have been due to the development of a vigorous campaign that encouraged parents to bring their children to the clinic for early treatment of impetigo with systemic antibiotics.

Through our ongoing statewide streptococcal surveillance program, we had gathered evidence that the epidemic serotypes had not been present in the state for at least five years prior to the outbreak, a situation similar to that found at Red Lake.[13] Both the 49-14 and the NT-14 organisms isolated from the cases appeared as new introductions at about the same time. Preliminary laboratory evidence suggests that the NT-14 organism differs from the 49-14 serotype, implying that the NT-14 organism may be a new nephritogenic strain. Futher bacteriologic studies of these organisms are under way.

After the epidemic arose in the Bethel region, the implicated nephritogenic organisms eventually became established in various other parts of Alaska to nearly the same extent as they had been in the Bethel region. However, there was only a small increase in the occurrence of symptomatic cases of acute glomerulonephritis in these areas after the apparent spread of the epidemic serotype. The absence of an epidemic in the presence of impetigo infected with nephritogenic streptococci has been observed in Trinidad,[17] and additional study of the organisms observed in this phenomenon may further elucidate the pathogenesis of this disease.

The medical, nursing, and laboratory staff of the Public Health Service Alaska Native Hospital in Bethel and the Streptococcal Surveillance Program of the Yukon-Kuskokwim Health Corp provided assistance. George Brenneman, MD, Phillip Barrett, MD, Douglas Cowgill, MD, Quentin Fisher, MD, Robert Hurwitz, MD, Benjamin Marchello, MD, Raymond Shields, MD, Leslie Boss, MT (ASCP), Carol Conlon, MT (ASCP), and Patricia Porter, MT (ASCP), provided assistance. Richard R. Facklam, PhD, and Lewis W. Wannamaker, MD, studied the strains involved in the epidemic and provided confirmatory serotyping.

References

1. Ferrieri P, Dajani AS, Wannamaker LW, et al: Natural history of impetigo: I. Site sequence of acquisition and familial patterns of spread of cutaneous streptococci. *J Clin Invest* 51:2851-2862, 1972.

2. Dillon HC Jr: Impetigo contagiosa: suppurative and non-suppurative complications: I. Clinical, bacteriologic, and epidemiologic characteristics of impetigo. *Am J Dis Child* 115:530-541, 1968.

3. Anthony BF, Kaplan EL, Wannamaker LW, et al: Attack rates of acute nephritis after type 49 streptococcal infection of the skin and of the respiratory tract. *J Clin Invest* 48:1697-1704, 1969.

4. Poon-King T, Mohammed I, Cox R, et al: Recurrent epidemic nephritis in South Trinidad. *N Engl J Med* 277:728-733, 1967.

5. Bjos G, Juhlin I, Moller H: Bacteriology and urinary examination in impetigo contagiosa. *Acta Derm Venereol* 53:481-486, 1973.

6. Edwards EA: Protocol for micro antistreptolysin O determinations. *J Bacteriol* 87:1254-1255, 1964.

7. Klein GG, Baker CN, Addison BV, et al: Micro test for streptococcal anti-deoxyribonuclease B. *Appl Microbiol* 18:204-206, 1969.

8. Ayoub EM, Wannamaker LW: Evaluation of the streptococcal deoxyribonuclease B and diphosphopyridine nucleotidase antibody tests in acute rheumatic fever and acute glomerulonephritis. *Pediatrics* 29:527-538, 1962.

9. Dillon HC Jr, Avery MS: Streptococcal immune responses in nephritis after skin infection. *Am J Med* 56:333-346, 1974.

10. Redys JJ, Hibbard EW, Borman EK: Improved dry-swab transportation for streptococcal specimens. *Public Health Rep* 83:143-149, 1968.

11. Lancefield RC: A serological differentiation of human and other groups of streptococci. *J Exp Med* 57:571-595, 1933.

12. Moody MD, Padula DL, Hall CT: Epidemiologic characterization of group A streptococci by T-agglutination and M-precipitation tests in the Public Health Laboratory. *Health Lab Sci* 2:149-162, 1965.

13. Kaplan EL, Anthony BF, Chapman SS, et al: Epidemic acute glomerulonephritis associated with type 49 streptococcal pyoderma: I. Clinical and laboratory findings. *Am J Med* 48:9-27, 1970.

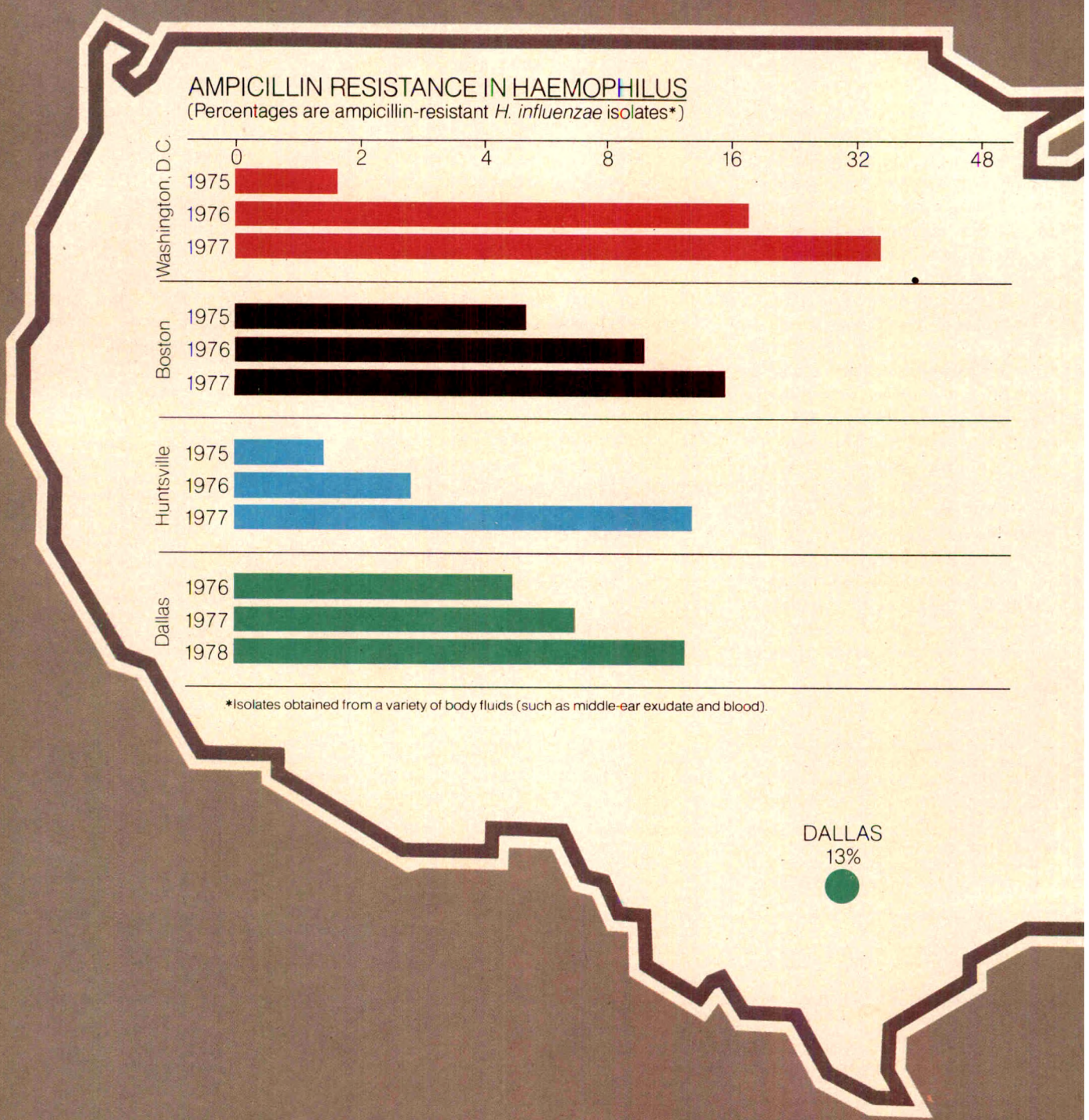
14. Lasch EE, Frankel V, Vardy PA, et al: Epidemic glomerulonephritis in Israel. *J Infect Dis* 124:141-147, 1971.

15. Anthony BF, Kaplan EL, Wannamaker LW, et al: The dynamics of streptococcal infections in a defined population of children: Serotypes associated with skin and respiratory infections. *Am J Epidemiol* 104:652-666, 1976.

16. Nelson KE, Bisno AI, Waytz P, et al: The epidemiology and natural history of streptococcal pyoderma: An endemic disease of the rural southern United States. *Am J Epidemiol* 103:270-283, 1976.

17. Ortiz JS, Finklea JF, Potter EV, et al: Endemic nephritis and streptococcal infections in South Trinidad. *Arch Intern Med* 126:640-646, 1970.

Increasing resistance o



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor®(cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PE CILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCL ING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor® (cefaclor, Lilly), should administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

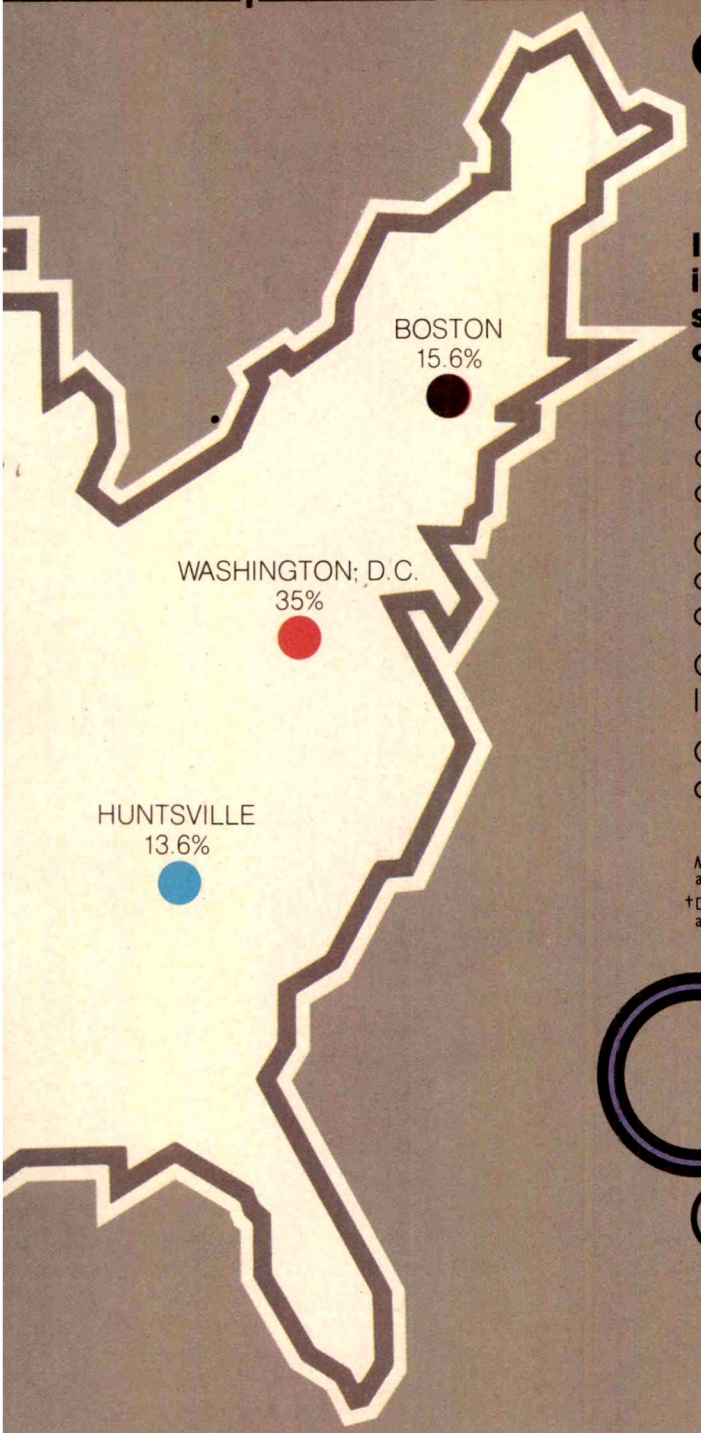
Precautions: If an allergic reaction to cefaclor occurs, t drug should be discontinued, and, if necessary, the pat should be treated with appropriate agents, e.g., pressc amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrow of nonsusceptible organisms. Careful observation of th patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported dur treatment with the cephalosporin antibiotics. In hemato logic studies or in transfusion cross-matching procedu when antiglobulin tests are performed on the minor sid in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it

Haemophilus influenzae in otitis media...

a valid concern



In many areas of the country, increasing numbers of *H. influenzae* show resistance to conventional antibiotic therapy.[1-3]

Ceclor is effective in the treatment of otitis media†, including that due to some ampicillin-resistant strains of *H. influenzae*.[4-9]

Ceclor has been shown to be clinically and bacteriologically effective in treating otitis media due to susceptible organisms.[10]

Ceclor is available in two pleasant-tasting liquids.

Ceclor provides effective single-agent antibiotic therapy for otitis media.

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

†Due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes*.

125-mg/5-ml and 250-mg/5-ml oral suspensions

Ceclor®

cefaclor

should be recognized that a positive Coombs test may be due to the drug.

Ceclor ® (cefaclor, Lilly) should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below:

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0703790]

References

1. J. Pediatr., *92*:889, 1978.
2. J. Pediatr., *94*:983, 1979.
3. J.A.M.A., *239*:320, 1978.
4. Antimicrob. Agents Chemother., *11*:470, 1977.
5. Antimicrob. Agents Chemother., *13*:584, 1978.
6. Antimicrob. Agents Chemother., *12*:490, 1977.
7. Current Chemotherapy, *II*:880, 1978.
8. Antimicrob. Agents Chemother., *8*:91, 1979.
9. Antimicrob. Agents Chemother., *13*:861, 1978.
10. Data on file, Eli Lilly and Company.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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Review

The Prostaglandins

Peter M. Olley, MD, Flavio Coceani, MD

During the last decade, the prostaglandins have attracted considerable research activity and have become of clinical importance in several disease states. It is probable that further clinical applications will develop in the future and, therefore, a review of our current knowledge of these biologically active compounds is timely. The reader should appreciate that information about the biosynthesis and metabolism of the prostaglandins (PGs) and related substances is increasing so rapidly that even the results of experiments performed recently have to be constantly reevaluated. What may seem to be true today may no longer be valid tomorrow!

"Prostaglandin" was the named coined by von Euler[1] in 1935 for an active substance found in lipid extracts of sheep seminal vesicles that both stimulated smooth muscle to contract and caused hypotension when injected into animals. Not all the compounds to be discussed in this article share the prostanoic acid skeleton, which is the essential component of PG structure; however, for convenience the term PG will be used in this review to designate the whole family of compounds.

Concurrent with von Euler's studies were those of Goldblatt[2,3] in England who also investigated the smooth muscle stimulating activity of seminal fluid from several species. Priority in describing a PG activity belongs to Kurzrok and Lieb[4] when they observed strong uterine relaxations or contractions in response to vaginal instillation of fresh semen in humans.

Further PG research was stimulated when Bergstrom et al[5,6] successfully crystallized minute amounts of PGE_1 and $PGF_{1\alpha}$ and with other collaborators elucidated their structure and that of several additional PGs. The 1970s have brought further major advances to the understanding of the family of PGs that will be discussed in the next section.

STRUCTURE

The PGs are 20-carbon unsaturated fatty acids whose structure comprises a cyclopentane ring with two aliphatic side chains. Each PG is designated by a letter dependent on its cyclopentane substituents and by a subscript numeral indicating the number of carbon-to-carbon double bonds present in the side chains. The "F" series in which the 9-hydroxyl group can potentially have one of two stereochemical orientations are further designated as being α or β. The β variant does not occur naturally. The thromboxanes (TX) differ from the PGs in having an oxane ring structure but share similar side chains and nomenclature. Prostacyclin (PGI_2) is a 6, 9-enol ether whose precise structure was recently elucidated (Fig 1).[7]

Prostaglandins are biosynthesized from dihomo-γ-linolenic acid (eicosatrienoic acid) and arachidonic acid (eicosatetranoic acid)[8,9] both of which are derived from the essential dietary fatty acid, linoleic acid. Synthesis from dihomo-γ-linolenic acid results in the "1" series of PGs, arachidonic acid is the precursor of the "2" series, whereas the "3" series are biosynthesized from eicosapentanoic acid.

The polyunsaturated fatty acid precursors are incorporated into phospholipids and, thus, are an important component of cell membranes. Prostaglandins have been found in all mammalian tissues studied, the predominant precursor present being arachidonic acid. Prostaglandins are not stored preformed but are synthesized and released as required. Arachidonic acid is split from the cell membrane phospholipids by an enzyme, phospholipase A_2,[10,11] and once released may be transformed via one of three different pathways (Fig 2).

The initial step always involves a site-specific incorporation of oxygen by a lipoxygenase-catalyzed reaction. Pathway 1 is the "classical" cyclooxygenase pathway and yields TXA_2, PGI_2, and the primary PGs (PGE_2, PGD_2, $PGF_{2\alpha}$) via the endoperoxide intermediates, PGG_2 and PGH_2. Pathways 2 and 3 are recent additions to the so-called PG system and yield a host of hydroxy, hydroperoxy, and epoxy products. These products in-

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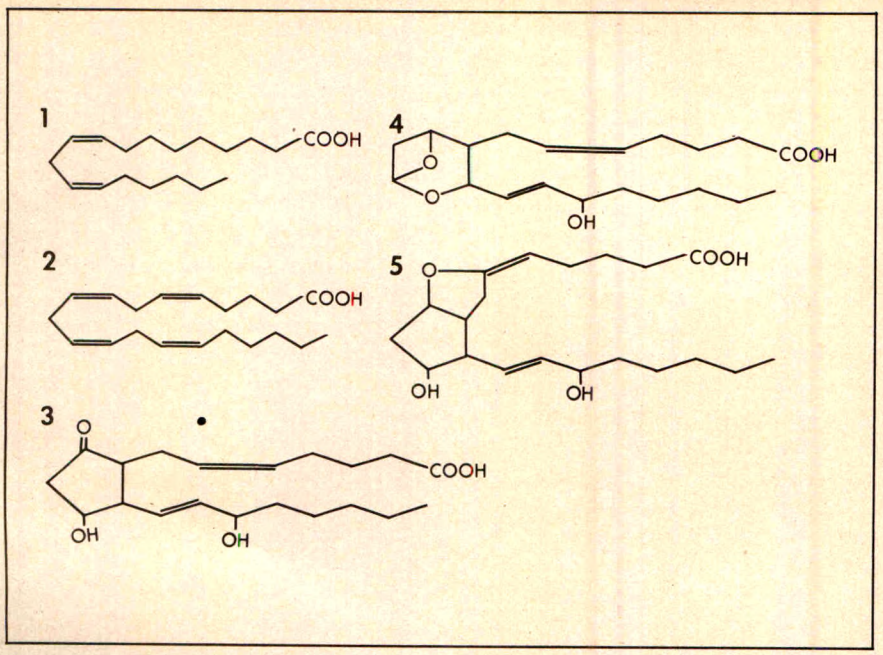
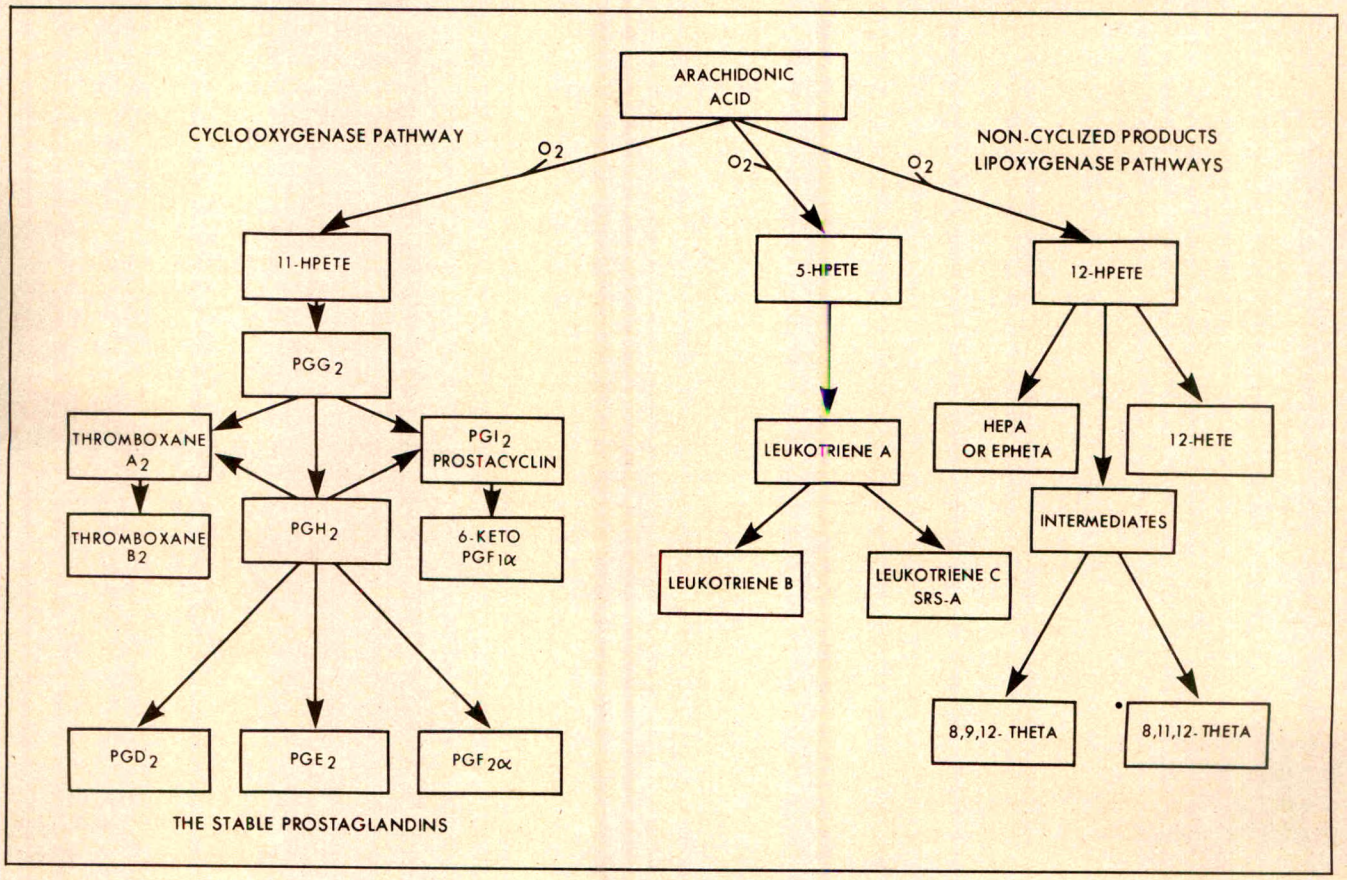


Fig 1.—Structure of linoleic acid (1), arachidonic acid (2), prostaglandin E_2 (3) thromboxane A_2 (4), and prostaglandin I_2 (prostacyclin) (5).

clude substances bearing three conjugated double bonds, the leukotrienes.[12,13] Although little is known of the occurrence and activity of noncyclized, oxygenated fatty acids in various tissues, the finding that leukotriene C is identical to slow-reacting substance A raises the possibility that pathways 2 and 3 may equal or exceed in importance the cyclooxygenase pathway. Because of these recent developments, the term "PG system" may not be appropriate to indicate the entire group of biologically active substances derived from arachidonic acid. Corey has proposed the alternative term of "eicosanoids."

The cyclooxygenase pathway has been much more extensively studied. Cyclooxygenase, located in the plasma membrane or endoplasmic reticulum, converts arachidonic acid by cyclization and inclusion of molecular oxygen[14,15] to unstable intermediates, the

Fig 2.—PG indicates prostaglandins; 11-HPETE, 11-hydroperoxy-5,8,12,14-e cosatetranoic acid; 5-HPETE, 5-hydroperoxy-6,8,11,14-eicosatetranoic acid; 12-HPETE, 12-hydroperoxy-5,8,10,14-eicosatetranoic acid; 12-HETE, 12-hydroxy-5,8,10,14-eicosatetranoic acid; HEPA, 10-hydroxy-11,12-epoxy-5,8,14-eicosatrienoic acid; 8,9,12-THETA, 8,9,12-trihydroxy-5,10,14-eicosatrienoic acid; 8,11,12-THETA, 8,11,12-trihydroxy-5,9,14-eicosatrienoic acid; and SRS-A, slow-reacting substance-A.



endoperoxides.[16,17] These intermediates have been designated PGG_2 and PGH_2. Prostaglandin G_2 is formed first and is rapidly converted to PGH_2. Both PGG_2 and PGH_2 are substrates for further transformations by several pathways. The biological half-life in aqueous solution of both these compounds is about five minutes at 37 °C. Transformation of PGH_2 to the stable primary PGs (PGD_2, PGE_2, and $PGF_{2\alpha}$) occurs either nonenzymatically or by isomerase or reductase enzymes that occur widely in mammalian tissues; their distribution is uneven and concentrations of a specific enzyme may vary according to the tissue under study.

In platelets, the lungs, the spleen, and probably in other tissues, PGG_2 and PGH_2 may be transformed to the non-PG metabolite TXA_2 that has a half-life of about 30 s and is further metabolized to the inactive TXB_2. Thromboxane A_2 aggregates platelets, constricts arteries, and accounts for most of the biological activity of so-called rabbit aorta contracting substance.[18]

The endoperoxides may also be enzymatically transformed to the unstable PGI_2 that prevents platelet aggregation and is a vasodilator.[19] At 37 °C and a physiological pH value, PGI_2 has a half-life of two to three minutes that can, however, be prolonged in an alkaline medium. The PGI_2 spontaneously hydrolyses to the much more stable 6-keto-$PGF_{1\alpha}$ that occurs in several tissues, including fetal and adult vessels, heart, lungs, and uterus.

The PGs and TXs are synthesized and released in response to cell stimulation. In a given tissue, the amount and type of PG produced depends on the nature and availability of substrate, on the spectrum of synthesizing enzymes present, and on the presence of cofactors. The pattern of PG production may be unique to a given tissue and may be altered by extrinsic stimuli, such as catecholamines, kinins, trauma, and hypoxia. In tissues where different PGs have opposing actions, this ability to alter the amount of individual PGs produced provides a mechanism for controlling physiological processes.

Further potential for modifying cell activity rests in the presence of enzymes capable of transforming one active PG to another.[8] The 9-keto-reductase that converts PGE_2 to $PGF_{2\alpha}$ has been identified in several tissues from different species, including human kidney and blood vessels. Prostaglandin D_2 can be converted to $PGF_{2\alpha}$ in sheep and humans. Recent work suggests that in the liver 6-keto-$PGF_{1\alpha}$, the relatively inactive metabolite of PGI_2, can be enzymatically converted to the biologically active 6-keto-PGE_1.[20]

Degrading enzymes capable of metabolizing $PGF_{2\alpha}$ and PGE_2 to less active compounds occur in many tissues. The lung, spleen, and kidney contain 15-hydroxyprostaglandin dehydrogenase that converts $PGF_{2\alpha}$ and PGE_2 to the much less active 15-keto derivatives, while a PG-Δ13-reductase is present in most organs.

E- and F-type PGs have an extremely short half-life in the circulation and are up to 95% inactivated during a single pass through the lungs.[21] Fetal and newborn sheep lungs also inactivate PGE_1 to a similar degree.[22] Pulmonary metabolites of PG undergo β-oxidation in the liver and kidney to 18- and 16-carbon compounds and the resulting inactive metabolites are excreted in the urine. ω-Oxidation also occurs in the liver.

INHIBITORS OF PG SYNTHESIS

Conversion of arachidonic acid to the endoperoxides by cyclooxygenase is inhibited by nonsteroidal anti-inflammatory drugs, such as aspirin and indomethacin. This action occurs in numerous species and in conditions varying from microsomal preparations of the enzyme through to whole organs or organisms. Measurements in man suggest that the usual therapeutic doses are sufficient to inhibit PG biosynthesis. Cyclooxygenase inhibition interferes not only with the formation of the stable PGs but also with that of the endoperoxides, TXA_2, and PGI_2; however, the lipoxygenase pathways are not blocked and production of their metabolites could be enhanced.

Moncada and Vane[23] have proposed that it is this enzyme inhibition that underlies the therapeutic actions of aspirin-like drugs in reducing fever, pain, and inflammation and the side effects of these agents are caused by concomitant suppression of PG biosynthesis required for normal cell activity. This attractive theory has been challenged by Smith[24] mainly on the grounds that salicyclic acid, as potent an anti-inflammatory agent as aspirin in vivo, has no inhibitory effect on cyclooxygenase in vitro. Furthermore, enzymes from differing tissues have varying sensitivities to aspirin-like drugs. The paradox of salicyclic acid remains to be resolved but the weight of evidence is in favor of the hypothesis proposed by Moncada and Vane.

Several more selective inhibitors are now under study. Imidazole and benzydamine hydrochloride interfere with thromboxane synthesis, whereas tranylcypromine and 15-hydroperoxyarachidonic acid inhibit PGI_2 production. (Rajtar and deGaetano[25] recently reported lack of selective inhibitory activity of tranylcypromine on vascular PGI_2 synthesis in the rat.) Such selective inhibitors may also divert arachidonic acid metabolism along unblocked pathways, thus increasing the formation of other metabolites.

Steroids and quinacrine hydrochloride also interfere with PG formation by preventing the release of substrate from membrane phospholipid by phospholipase A_2[26] and perhaps by reducing transport of the nonesterified arachidonic acid to the cyclooxygenase.

PHYSIOLOGICAL FUNCTION OF PGs

Despite the enormous volume of research in the last decade the role and importance of PGs in cell physiology remains unclear and seemingly attractive hypotheses based on the known actions of the stable PGs are now being reassessed to take into account the TX and PGI_2 pathways. The cyclic nucleotides and calcium ion are clearly universal and interrelated second messengers in the activation of particular cell types responding to specific extracellular stimuli. The Yin-Yang hypothesis postulates that the intracellular ratio of cyclic adenosine 3′,5′-monophosphate (cAMP) to cyclic

guanosine 3′,5′-monophosphate (cGMP) controls cells function. For example, in vascular smooth muscle cAMP causes relaxation, whereas cGMP produces contraction.[27,28]

E-type PGs elevate AMP concentrations in several tissues by stimulating adenylcyclase, whereas in contrast $PGF_{2\alpha}$ stimulates cGMP formation in a variety of tissues. More recently, the TXs and PGI_2 have been shown to affect cellular cyclic nucleotide concentrations.[29,30] Even though a simple relationship between the stable PGs and intracellular cAMP and cGMP levels now seems unlikely, further studies of the role of the expanded PG family in modifying intracellular events seems more than justified.

The PGs have also been implicated as modulators of sympathetic neurotransmission.[31-33] Hedqvist[34] has reviewed the evidence showing that exogenous PGE compounds may affect sympathetic neurotransmission by acting at both prejunctional and postjunctional levels. At the postjunctional level, their action may be inhibitory or stimulatory, depending on the tissue studied and/or the dose of PG used. An inhibitory presynaptic action has been shown in spleen, heart, and vas deferens. Nerve stimulation increases both formation and release of PGE compounds in many sympathetically innervated tissues. Based on these findings, Hedqvist has proposed that endogenous PGs of the E series modulate sympathetic neurotransmission by a feedback mechanism. This proposal generated numerous additional studies to obtain evidence in support of, or against, Hedqvist's hypothesis (reviewed by Westfall[33]). In summary, it seems that although the predominant effect of E-type PGs is inhibition of norepinephrine release, this action is not universal and there are examples of tissues in which there is no effect or in which responsiveness to nerve stimulation is enhanced.

Prostaglandin $F_{2\alpha}$ seems to have no effect or to enhance the effector cell response to nerve stimulation and exogenous norepinephrine but at present seems to be much less important than E_2 in the control of sympathetic neurotransmission.[33] Ultimately, the PGs may influence cell activity by their action on calcium transport both within the cell where TXA_2 may convey calcium unidirectionally from the sequestered sites in the dense tubular system into the cytoplasm and across the cell membrane.[35]

Arachidonic acid metabolites with their rapid biosynthesis are equally rapid inactivation coupled with their diverse actions seem ideally endowed to act as modulators of intracellular events and perhaps as messengers between adjacent cells. They seem less fitted to a role as circulating hormones, although they could be carried in the blood bound to protein and then released to act on a distant target organ or cell. While their role in diverse organs and tissue remains under active investigation, a unifying concept awaits elucidation.

ASSAY METHODS

Because PGs are not stored in tissues but are rapidly biosynthesized, degraded measurements of tissue concentrations must be interpreted with caution. Three types of quantitative assays for the PGs are in current use.

Bioassay can be performed in vitro or in vivo. The in vitro "cascade" uses several different organs superfused consecutively by the same sample.[36] The specificity of each organ can be increased by pretreatment with specific antagonists against other biologically active materials and by prior purification of the sample. The advantages of bioassay are that it is the only possible method for screening labile unknowns and is reasonably sensitive (can detect < 1 ng of pure active compound). On the other hand, it cannot be used to quantitate biologically inactive metabolites; it has a low-sample capacity and even with pretreatment the specificity may be questionable. The results may be affected by metabolism of the test compounds by one or more of the organs, a danger that can be partially overcome by changing the order of the organs.

Radioimmunoassay (RIA)[37-39] is relatively cheap and sensitive (detects < 50 pg) and with proper precautions can be fairly specific. The technique is relatively simple and has a large-sample capacity. One must be aware of interpretational errors from cross-reactivity. Granstrom[38] has warned against the "kit mentality" in the use of RIA.

Gas chromatography-mass spectrometry (GC-MS) is the reference method. Introduced by Samuelsson and associates for PGE_1,[40] it has now been extended to a large number of related compounds.[41] Highly specific, GC-MS permits simultaneous analysis of several compounds with a high sensitivity (50 to 250 pg). It has the disadvantages of being expensive and time consuming. Sample size is low and it requires elaborate purification procedures.

Although it is possible to measure various PG concentrations in plasma, serum, or urine, one must be aware of the great fluctuations in concentrations that occur. Hillier has discussed the sources of error in such measurements.[42]

Levels of $PGF_{2\alpha}$ are elevated in sheep uterine venous plasma at parturition,[43] while the concentration of PGE in fetal plasma is raised shortly before delivery as are those in amniotic fluid.[44] The concentrations of 6-keto-$PGF_{1\alpha}$ are also elevated in maternal and fetal plasma and in amniotic fluid during late pregnancy and parturition in sheep.[45] These findings suggest a role for the PGs in the control of fetal and placental hemodynamics and of parturition. Mitchell et al[46,47] studied plasma PG levels during early neonatal life in term infants and in preterm infants before and after treatment for patent ductus arteriosus. Prematurity per se was not associated with substantially different levels of PGE, PGF, or PGF metabolite but in nine premature infants with patent ductus arteriosus and congestive heart failure levels were significantly higher ($P < .01$) and did not decrease after surgical ligation of the ductus arteriosus. Hyaline membrane disease is also associated with the noticeable elevation of plasma PGF level, which is a vasoconstrictor and may contribute to the circulatory problem in these infants.[48] Levels of PGE in cord blood are substantially higher than those in adults, but by 48

to 72 hours decrease to concentrations substantially below those in adults. Thereafter, they increase with age, but remain less than adult levels.[49]

PGs, INFLAMMATION, AND FEVER

Inflammation is associated with the local release of a number of vasoactive substances, including histamine, 5-hydroxytryptamine (5-HT), slow-reacting substance of anaphylaxis, bradykinin, TXA_2, E and F PGs, lysosomal enzymes, and chemotaxins. Anti-inflammatory agents have little effect on histamine, 5-HT, and bradykinin actions, but by antagonizing PG biosynthesis, they prevent inflammatory responses mediated by arachidonic acid metabolites.

The nature of the inflammatory response depends on tissue sensitivity and on the spectrum and sequence of mediator released. In anaphylactic shock, multiple mediators are released simultaneously,[50] whereas subcutaneous carrageenin in the rat invokes a sequential release of histamine, bradykinin, and then PGs.[51] The metabolite of PGI_2, 6-keto-$PGF_{1\alpha}$, has been found in chronic granulomas.[52] One of the metabolites of the lipoxygenase pathway is highly chemotactic.[53]

The E-type PGs (also F-type and PGI_2 to a lesser extent) cause erythema from pooling in relaxed vessels and edema from increased vascular permeability in postcapillary and collecting venules. Low concentrations of PGE_1 subdermally cause hyperalgesia, whereas higher doses cause long-lasting pain. Prostaglandins seem to sensitize sensory nerves to chemical stimulation by other substances and to exacerbate histamine-induced pruritus. Aspirin and related substances, by preventing PG generation, relieve the symptoms of inflammation.[54] While Kuehl et al[55] have proposed that the endoperoxides, rather than the stable PGs, occupy the central role in the mechanism of inflammation, this does not nullify the current concepts of the action of aspirin.

The E-type PGs are the most powerful pyretic known and act in a dose-dependent fashion when injected into the cerebral ventricles or the anterior hypothalamus[56,57]; the onset of fever is almost immediate and lasts several hours. Arachidonic acid also induces fever, but with some latency, this effect is blocked by aspirin. Prostaglandin E is generated during spontaneous fever and concentrations in the CSF rise. Patients given PGE_2 or $PGF_{2\alpha}$ to induce abortion[58] or to maintain patency of the ductus arteriosus frequently become febrile.[59] Aspirin and related drugs inhibit the generation of PGs in the CNS during fever and prevent pyrogen-induced fever.[60]

One may conclude that it is highly probable that metabolites of arachidonic acid are intimately involved in the pathogenesis of inflammation, pain, and fever and that the beneficial effect of aspirin and related drugs on these symptoms is due to cyclooxygenase inhibition.

PGs and Ductus Arteriosus

The ductus arteriosus contains a cyclooxygenase[61-63] and possibly lipoxygenase[64] as well. Prostaglandin I_2 seems to be the major product as in other vessels. Cyclooxygenase inhibition with indomethacin or ibuprofen constricts the fetal ductus arteriosus in vitro and in vivo.[65] This action is more noticeable in premature animals and is fully reversed by treatment with PGE_1 or PGE_2. On the basis of this evidence, patency of the fetal ductus arteriosus is now regarded as an active state sustained by a continuous intramural production of PG. Prostaglandin E_2 is the prime candidate for this role.[65] However, PGI_2 may acquire a more central function should future investigations demonstrate the presence in ductal tissue of an enzyme system able to convert 6-keto-$PGF_{1\alpha}$ to 6-keto-PGE_1. This latter compound is a potent antithrombotic and ductus-relaxing agent.[66]

The postnatal increase in blood oxygen content initiates closure of the ductus arteriosus, although it is not clear whether this is a direct action or involves some vasoactive mediator. Both $PGF_{2\alpha}$[67] and TXA_2[68] have been proposed for this role, but the balance of evidence is against this possibility. An alternative possibility is that oxygen-induced contraction results from a withdrawal of the tonic-relaxing influence of endogenous PGs.

Clinical use of these experimental data has been made in newborn infants with heart disease and in premature babies with a patent ductus arteriosus and significant left-to-right shunting. A continuous infusion of PGE_1 (0.05 to 0.1 μg/kg/min) given either intraarterially or intravenously maintains ductal patency in infants with ductus-dependent cardiac malformations, allowing time for reversal of hypoxia, correction of metabolic acidosis, and arrangement of semi-elective surgical intervention.[69]

In contrast, indomethacin (0.3 to 0.6 mg/kg/24 hr) has been used successfully to close the ductus arteriosus in premature infants. Reported success rates have varied and the factors determining responsiveness remain obscure.[70-72] Actual age at time of therapy,[73] concomitant drug therapy,[74] or circulating PG levels may all be important. Failure of drug absorption does not seem to be a factor.[75] The final place for indomethacin, or, in the future, more specific synthesis blockers, in the problem ductus of the premature is still under evaluation and must be compared with the excellent results now being achieved by the surgeons.

PGs AND LUNGS

The products of arachidonic acid metabolism within the lungs include PGD_2, PGE_2, $PGF_{2\alpha}$, TXB_2, and 6-keto-$PGF_{1\alpha}$, the latter implying active synthesis of PGI_2. The physiologic importance of these compounds to both normal bronchomotor tone and to the control of the pulmonary circulation is currently under active investigation.[76,77]

Exogenous PGE_1 is a pulmonary vasodilator in both neonatal[78] and adult animals, whereas $PGF_{2\alpha}$ is a constrictor. Prostaglandin D_2 has a constrictor action, whereas PGE_2 has been found to be both a constrictor[79] and a dilator.[78] Kadowitz et al[79] have attempted to explain the somewhat anomalous action of PGE_2 on the basis of conversion to $PGF_{2\alpha}$. Prostaglandin I_2 has been reported to be a dilator in the cat.[80] In conscious newborn lambs, PGD_2 and $PGF_{2\alpha}$ are direct pulmonary vasoconstrictors, whereas PGE_1, PGE_2, and PGI_2 are direct vasodila-

tors. During hypoxia, the PGE_1 and PGI_2 effects are enhanced while the constrictor action of PGD_2 and $PGF_{2\alpha}$ is diminished. Hypoxia also lowers the threshold for PGI_2-induced dilation.[81]

Although the E-type PGs and PGI_2 are both local dilators, they differ in that the systemic dilatory effects of the E-type agents exceed their pulmonary effects, whereas under hypoxia the opposite occurs with PGI_2. Thus, PGs can act locally on pulmonary vascular smooth muscle in vivo and their action is influenced by the level of oxygenation or baseline vascular tone.[81]

A bolus injection of indomethacin induces acute pulmonary vasoconstriction. Chronic indomethacin therapy neither alters baseline pulmonary tone nor the pulmonary vascular responses to hypoxia, acetylcholine, bradykinin, or histamine. However, pretreatment with indomethacin does abolish the pulmonary effects of a further intravenous dose of the drug.[82] These results suggest that although the PGs may have a role in the control of pulmonary vascular tone, they are not essential to that control.

Because of its apparently selective pulmonary vasodilating effects, PGI_2 is of potential value in the therapy of conditions in which pulmonary vasoconstriction plays a role. A continuous infusion of PGI_2 was successful in lowering pulmonary resistance in a newborn with persistent fetal circulation syndrome.[83]

The effects of the PGs on pulmonary vessels are paralleled by their effects on bronchomotor tone. Prostaglandin $F_{2\alpha}$ is a potent bronchoconstrictor, especially in asthmatics. Prostaglandin E_1 and E_2 are bronchodilators, their action being unaffected by α- or β-adrenoreceptor blockade. Aspirin and indomethacin decrease the intrinsic tone of guinea pig tracheal rings, whereas TXA_2 and the endoperoxides are ten times more active than $PGF_{2\alpha}$ in causing contraction in the same experimental model.[77]

Aspirin-induced asthma may result from inhibition of endogenous PGE_2 production; with the loss of its bronchodilator effect, the bronchi constrict in response to histamine and other mediators.[84] Unfortunately, the therapeutic use of aerosolized E-type PGs in asthmatic subjects has proved disappointing. Not only is the response unpredictable but they cause consistent irritation of the upper airways. Possibly PGE_1 or PGE_2 analogues may prove to be more useful.

PGs IN REPRODUCTION

Arachidonic acid is relatively abundant in reproductive tissues, including umbilical cord, fetal membranes, placenta, myometrium, decidua, amniotic fluid, and maternal and fetal plasma.[85] Biosynthesis of PGE_2 has been demonstrated in umbilical cord, fetal membranes, decidua, and myometrium. Prostaglandin metabolism occurs in the chorion and placenta. Exogenous PGs contract the human uterus by a direct action on myometrial cells, PGE_2 being some ten times more potent than $PGF_{2\alpha}$. Prostaglandins are luteolytic in many subprimate species but not in humans. Prostaglandin concentrations in blood and amniotic fluid are raised during labor in many species, including humans, and decrease abruptly when labor is over.[86]

Prostaglandin $F_{2\alpha}$ effectively terminates pregnancy at all stages of gestation whether given vaginally, extraamniotically or intraamniotically, or intramuscularly, and has been used clinically to induce labor at term and second-trimester abortions. When used to induce term labor, especially in nulliparous women, there is an increased risk of hypertonus and fetal bradycardia, than during spontaneous labor or surgical induction.[87] Prostaglandin E_2 and its 15-methyl analogue given orally are also under evaluation for labor induction.

In pregnant women and monkeys, aspirin and related compounds prolong gestation and delay parturition[88,89] and oral indomethacin has been used to treat women in premature labor.[90-92] Karim[91] has reviewed the possible hazards to the fetus from administration of PG synthetase inhibitors to the mother that may include teratogenicity, increased incidence of stillbirth; circulatory effects, such as intrauterine closure of the ductus arteriosus and fetal hemorrhage.[91] Pulmonary hypertension, premature closure of the ductus arteriosus, and tricuspid insufficiency have been reported in the infants of mothers who received indomethacin.[93,94] Carefully conducted clinical trials in a few centers are clearly necessary to assess the true risks to the fetus of this approach to premature labor.

PGs, PLATELETS, AND VASCULAR INTEGRITY

Much of the basic research on the PG system has been done on platelets and on the interactions between platelets and vessel walls. It now seems that PGI_2 and TXA_2 are more important to these interactions than are the stable PGs. Prostaglandin E_1, but paradoxically not PGE_2, inhibits platelet aggregation induced by adenosine diphosphate, collagen, or adrenaline.[95] However, little PGE_1 is likely to be formed in platelets that contain hardly any of its precursor, dihomo-γ-linolenic acid. When tested, the PG endoperoxides were found to be strongly proaggregatory and this action was subsequently found to be due to transformation to TXA_2.[96] Thromboxane A_2 also proved to be a potent arterial vasoconstrictor. In contrast, PGI_2, the major arachidonic acid metabolite in vessel walls, has a strong antiaggregatory action on platelets as well as being a powerful vasodilator. Generation of PGI_2 within the vessel wall and from endoperoxides released by platelets may well be the physiologic mechanism that protects the damaged vessel wall from deposition of platelet aggregates. The opposing actions of TXA_2 and PGI_2 suggests a homeostatic mechanism that preserves vascular integrity.[97]

Prostacyclin can be released from the lung into arterial blood. Moncada and Vane[97] have suggested that circulating PGI_2 may have a continuing role in preventing platelet aggregation by constantly activating platelet adenylate cyclase. Furthermore, PGI_2 also disaggregates platelet clumps as well as discouraging their formation, this could be of special protective value in the pulmonary microcirculation in which platelets are trapped.

New knowledge about arachidonic acid metabolites and platelet aggrega-

tion has led to a better understanding of the mode of action of several antithrombotic agents. Aspirin irreversibly inactivates platelet cyclooxygenase by acetylation of the active sites, thereby preventing TXA_2 formation,[98] while dipyridamole potentiates the action of PGI_2 on platelets by inhibition of phosphodiesterase.[99] Burch et al[100] have shown that cyclooxygenase in human aorta and coronary artery microsomes is some 250 times less sensitive to aspirin than the enzyme in intact platelets and some 60 times less sensitive than the enzyme measured in a platelet microsomal fraction. On the basis of their in vitro data, they predict that small oral doses of aspirin are sufficient to inhibit platelet TX production, while having little action on aorta or coronary artery PGI_2 production. If confirmed, this finding is of great importance to the various trials of antithrombotic agents currently in progress.

How important are arachidonic acid metabolites to normal hemostasis? Malmsten et al[101] described a patient with a hemostatic defect from platelet cyclooxygenase deficiency. Platelets from rats fed dihomo-γ-linolenic acid showed decreased aggregation in response to collagen or epinephrine.[102] However, against the PGs having a central role in hemostasis is the finding that thrombin induces complete platelet aggregation and release, in both aspirin-treated platelets and in platelets from the patient with cyclooxygenase deficiency. Majerus[103] has suggested that aspirin induces a mild defect in platelet function that increases the threshold for platelet aggregation and release reaction.

However, this may be of clinical importance. Platelet aggregation in premature infants given indomethacin to induce ductal closure was grossly abnormal for two to four days after administration and in one of four infants studied by Friedman et al,[104] gastrointestinal bleeding and transient renal dysfunction developed.

The relationship between diet and the incidence of myocardial infarction remains the subject of intensive research. Eskimos have a low incidence of myocardial infarction and an increased tendency to bleed and this could be related to the high proportion of eicosapentanoic acid in their diet that is mainly derived from marine animals. Eicosapentanoic acid is the precursor of the three series of PGs and can be transformed to an antiaggregatory agent, probably PGI_3, whereas TXA_3, although formed, is nonaggregatory. Thus, a diet high in eicosapentanoic acid and relatively low in linoleic and arachidonic acid may help to protect against intravascular thrombosis. Dietary linoleic acid is converted to arachidonic acid in the body and is essential for the formation of membrane phospholipids. Further studies of the influence of these precursors on the balance between platelet aggregation and nonaggregation are clearly of great importance.

OTHER CLINICAL POSSIBILITIES

Essential fatty acid deficiency has been noted in cystic fibrosis,[105] and PG synthesis may be reduced either secondary to diminished availability of linoleic acid[106] or to impaired oxidation of fatty acids.[107] Chase and Dupont[108] found that the production of $PGF_{2\alpha}$ from linoleic acid is higher in children with cystic fibrosis than in controls, even though the children with cystic fibrosis had lower plasma levels of linoleic acid. Prostaglandin $F_{2\alpha}$ is both a pulmonary vasoconstrictor and a bronchoconstrictor and its overproduction over a long period of time could be important in the pathophysiology of cystic fibrosis. In a trial of intravenously administered soya bean emulsion (intralipid) in seven children with cystic fibrosis treated for a year or more, Elliott[106] observed remarkably better health than in others with cystic fibrosis not treated with intralipid. These results require confirmation in properly randomized clinical trials.

Increased PG synthesis has been found in children with diabetes mellitus who had elevated blood levels of PGE_2, $PGF_{2\alpha}$, and linoleic acid[109] and may be related to the vascular complications inflicting diabetics.

Overproduction of E-type PGs has been proposed to explain Bartter's syndrome, which is characterized by hypokalemic alkalosis, increased plasma renin activity and aldosterone, juxtaglomerular cell hyperplasia, low or normal blood pressure, and decreased sensitivity to angiotensin.[110] Based on this hypothesis, PG synthetase inhibitors have been used to treat Bartter's syndrome in both adults and children with successful reversal of clinical and biochemical abnormalities.[111,112]

CONCLUSION

This article is of necessity incomplete. Reviews of the importance of the PGs to the nervous system[60] and in renal physiology[113] have been published recently. The progressive unfolding of the PG story, doubtless still far from complete, enforces a constant reappraisal of concepts, theories, and apparently established facts. Indeed, even the name "prostaglandins" is in jeopardy and may be superseded by the more embrassive term "eicosanoids."

Although the physiologic role of the arachidonic acid metabolites remains uncertain, a number of clinical applications have emerged. The next decade will undoubtedly bring further exciting developments in this field.

Nonproprietary Names and Trademarks of Drugs

Dipyridamole—*Persantine.*
Ibuprofen—*Motrin.*

References

1. Von Euler US: On the specific vaso-dilating and plain muscle stimulating substances from accessory genital glands in man and certain animals. *J Physiol* 88:213-234, 1936.
2. Goldblatt MW: A depressor substance in seminal fluid. *J Soc Chem Ind* 52:1056-1057, 1933.
3. Goldblatt MW: Properties of human seminal plasma. *J Physiol* 84:208-218, 1935.
4. Kurzrok R, Lieb CC: Biochemical studies of human semen: II. The action of semen on the human uterus. *Proc Soc Exp Biol Med* 28:268-272, 1930.
5. Bergstrom S, Ryhage R, Samuelsson B, et al: The structure of prostaglandin E_1, $F_{1\alpha}$ and $F_{1\beta}$. *J Biol Chem* 238:3555-3564, 1963.
6. Bergstrom S, Samuelsson B: Prostaglandins. *Ann Rev Biochem* 34:101-108, 1965.
7. Johnson RA, Morton DR, Kinner JH, et al: Chemical structure of prostaglandin X (Prostacyclin). *Prostaglandins* 12:915-928, 1976.
8. Lands WEM: The biosynthesis and metabolism of prostaglandins. *Ann Rev Physiol* 41:633-652, 1979.
9. Samuelsson B, Goldyne M, Granstrom E, et

al: Prostaglandins and thromboxanes. *Am Rev Biochem* 47:997-1029, 1978.

10. Grieves SA, Liggins GC: Phospholipase A activity in human and ovine uterine tissues. *Prostaglandins* 12:229-241, 1976.

11. Schwarz BE, Schultz FM, MacDonald PC, et al: Initiation of human parturition: IV. Demonstration of phospholipase A_2 in the lysosomes of human fetal membranes. *Am J Obstet Gynecol* 125:1089-1092, 1976.

12. Borgeat P, Samuelsson B: Arachidonic acid metabolism in polymorphonuclear leucocytes: Unstable intermediate in formation of dihydroxy acids. *Proc Natl Acad Sci USA* 76:3213-3217, 1979.

13. Samuelsson B, Borgeat P, Hammarstrom S, et al: Introduction of a nomenclature: Leukotrienes. *Prostaglandins* 17:785-787, 1979.

14. Ramwell PW, Leovey EMK, Sintetos AL: Regulation of arachidonic acid cascade. *Biol Reprod* 16:70-87, 1977.

15. Pace-Asciak CR: Oxidative biotransformation of arachidonic acid. *Prostaglandins* 13:811-817, 1977.

16. Nugteren DH, Hazelhof E: Isolation and properties of intermediates in prostaglandin biosynthesis. *Biochim Biophys Acta* 326:448-461, 1973.

17. Hamberg M, Svensson J, Wakabayashi T, et al: Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. *Proc Natl Acad Sci USA* 71:345-349, 1974.

18. Hamberg M, Svensson J, Samuelsson B: Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc Natl Acad Sci USA* 72:2994-2998, 1975.

19. Moncada S, Vane JR: *The Discovery of Prostacyclin—A Fresh Insight Into Arachidonic Acid Metabolism*, ed 2. New York, Academic Press Inc, 1977, pp 155-177.

20. Wong P-Y-K, Malik KU, Sun FF, et al: *Hepatic Metabolism of Prostacyclin (PGI_2) in the Rabbit: Formation of a Potent Inhibitor of Platelet Aggregation.* Washington, Proceedings Fourth International Conference on Prostaglandins, 1979, p 127.

21. Ferreira SH, Vane JR: Prostaglandins: Their disappearance from and release into the circulation. *Nature* 216:868-873, 1967.

22. Olley PM, Coceani F, Kent G: Inactivation of prostaglandin E_1 by lungs of the fetal lamb. *Experientia* 30:58-59, 1974.

23. Moncada S, Vane JR: Mode of action of aspirin-like drugs, in Stollerman GH (ed): *Advances in Internal Medicine.* Chicago, Year Book Medical Publishers, 1979, pp 1-22.

24. Smith MJH: Aspirin and prostaglandins: Some recent developments. *Agents Actions* 8:427-429, 1978.

25. Rajtar G, deGaetano G: Tranylcypromine is not a selective inhibitor of prostacyclin in rats. *Thrombosis Res* 14:245-248, 1979.

26. Gryglewski RJ, Panczenko B, Korbut R, et al: Corticosteroids inhibit prostaglandin release from perfused mesenteric blood vessels of rabbit and from perfused lungs of sensitized guinea pig. *Prostaglandins* 10:343-356, 1975.

27. Goldberg ND, O'Dea RF, Haddox MK: Cyclic GMP. *Adv Cyclic Nucleotide Res* 3:155-223, 1973.

28. Kuehl FA Jr, Cirillo VJ, Ham EA, et al: The regulatory role of the prostaglandins on the cyclic 3′, 5′-AMP system. *Adv Biosci* 9:155-172, 1972.

29. Miller OV, Gorman RR: Modulation of platelet cyclic nucleotide content by PGE_1 and the prostaglandin endoperoxide PGG_2. *J Cyclic Nucl Res* 2:79-87, 1976.

30. Tateson JE, Moncada S, Vane JR: Effects of prostacyclin (PGX) on cyclic AMP concentrations in human platelets. *Prostaglandins* 13:389-397, 1977.

31. Brody MJ, Kadowitz PJ: Prostaglandins as modulators of the autonomic nervous system. *Fed Proc* 33:48-60, 1974.

32. Hedqvist P: Prostaglandin mediated control of sympathetic neuroeffector transmission. *Adv Biosci* 9:461-473, 1973.

33. Westfall TC: Local regulation of adrenergic neurotransmission. *Physiol Rev* 57:659-728, 1977.

34. Hedqvist P: Studies on the effect of prostaglandins E_1 and E_2 on the sympathetic neuromuscular transmission in some animal tissues. *Acta Physiol Scand* suppl 345, 1970, pp 1-40.

35. Gerrard JM, Townsend D, Stoddard S, et al: The influence of prostaglandin G_2 on platelet ultrastructure and platelet secretion. *Am J Pathol* 86:99-115, 1977.

36. Vane JR: The release and fate of vaso-active hormones in the circulation. *Br J Pharmacol* 35:209-242, 1969.

37. Granstrom E, Kindahl H: Radioimmunoassays for prostaglandin metabolites. *Adv Prostaglandin Thromboxane Res* 1:81-92, 1976.

38. Granstrom E: Assay methods for PGs and thromboxane. *Prostaglandins Thera* 5:3-4, 1979.

39. Samuelsson B, Goldyne M, Granstrom E, et al: Prostaglandins and thromboxanes. *Ann Rev Biochem* 47:997-1029, 1978.

40. Samuelsson B, Hamberg M, Sweeley CC: Quantitative gas chromatography of prostaglandin E_1 at the nanogram level: Use of deuterated carrier and multiple-ion analyzer. *Anal Biochem* 38:301-304, 1970.

41. Green K, Hamberg M, Samuelsson B: Quantitative analysis of prostaglandins and thromboxanes by mass spectrometric methods. *Adv Prostaglandin Thromboxane Res* 1:47-58, 1976.

42. Hillier K: Prostaglandins and thromboxanes: Pharmacologic and biosynthetic aspects. *Sem Perinatol* 2:197-210, 1978.

43. Liggins GC, Fairclough RJ, Grieves SA, et al: The mechanism of initiation of parturition in the ewe. *Rec Prog Horm Res* 29:111-159, 1973.

44. Challis JRG, Hart I, Louis TM, et al: Prostaglandins in the sheep fetus: Implications for fetal function. *Adv Prostaglandin Thromboxane Res* 2:115-132, 1978.

45. Mitchell MD, Ellwood DA, Anderson ABM, et al: Elevated concentrations of 6-keto-prostaglandin $F_{1\alpha}$ in fetal and maternal plasma and amniotic fluid during ovine parturition. *Prostaglandins Med* 1:265-266, 1978.

46. Mitchell MD, Lucas A, Etches PC, et al: Plasma prostaglandin levels during early neonatal life following term and pre-term delivery. *Prostaglandins* 16:319-325, 1978.

47. Lucas A, Mitchell MD: Plasma prostaglandins in pre-term neonates before and after treatment for patent ductus arteriosus. *Lancet* 2:130-132, 1978.

48. Mitchell MD, Lucas A, Whitfield M, et al: Selective elevation of circulating prostaglandin concentrations in hyaline membrane disease in pre-term infants. *Prostaglandins Med* 1:207-212, 1978.

49. Siegler RL, Walker MB, Crouch RH, et al: Plasma prostaglandin E concentrations from birth through childhood. *J Pediatr* 91:734-737, 1977.

50. Piper PJ, Vane JR: The release of prostaglandins from lung and other tissues. *Ann NY Acad Sci* 180:363-385, 1971.

51. Willis AL: Release of histamine, kinin and prostaglandins during carageenin-induced inflammation in the rat, in Mantegazza P, Horton EW (eds): *Prostaglandins, Peptides and Amines*, ed 2. New York, Academic Press Inc, 1969, pp 33-38.

52. Chang WC, Murota S, Matsuo M, et al: A new prostaglandin transformed from arachidonic acid in carageenin-induced granuloma. *Biochem Biophys Res Commun* 72:1259-1264, 1976.

53. Turner SR, Tainer JA, Lynn WS: Biogenesis of chemotactic molecules by the arachidonate lipoxygenase system of platelets. *Nature* 257:680-681, 1975.

54. Moncada S, Vane JR: Mode of action of aspirin-like drugs. *Adv Intern Med* 24:1-22, 1979.

55. Kuehl FA Jr, Humes JL, Egan RW, et al: Role of prostaglandin endoperoxide PGG_2 in inflammatory processes. *Nature* 265:170-173, 1977.

56. Feldberg W, Saxena PN: Fever produced by prostaglandin E_1. *J Physiol* 217:547-556, 1971.

57. Potts WJ, East PF: Effects of prostaglandin E_2 on the body temperature of conscious rats and cats. *Arch Int Pharmacodyn* 197:31-36, 1972.

58. Hendricks CH, Brenner WE, Ekbladh V, et al: Efficacy and tolerance of intravenous prostaglandins $F_{2\alpha}$ and E_2. *Am J Obstet Gynecol* 111:564-579, 1971.

59. Olley PM, Coceani F, Rowe RD: The role of prostaglandin E_1 and E_2 in the management of neonatal heart disease. *Adv Prostaglandin Thromboxane Res* 4:325-333, 1978.

60. Coceani F: The role of prostaglandins in the central nervous system. *Ann Rev Physiol* 41:669-684, 1979.

61. Pace-Asciak CR, Rangaraj G: Prostaglandin biosynthesis and catabolism in the lamb ductus arteriosus, aorta and pulmonary artery. *Biochim Biophys Acta* 529:13-20, 1978.

62. Powell WS, Solomon S: Biosynthesis of prostaglandins and thromboxanes in fetal tissues. *Adv Prostaglandin Thromboxane Res* 4:61-74, 1978.

63. Clyman RI, Mauray F, Koerper MA, et al: Formation of prostacyclin (PGI_2) by the ductus arteriosus of fetal lambs at different stages of gestation. *Prostaglandins* 16:633-642, 1978.

64. Moncada S, Herman AG, Higgs EA, et al: Differential formation of prostacyclin (PGX or PGI_2) by layers of the arterial wall: An explanation for the antithrombotic properties of vascular endothelium. *Thromb Res* 11:323-344, 1977.

65. Coceani F, Olley PM: Role of prostaglandins, prostacyclin, and thromboxanes in the control of prenatal patency and postnatal closure of the ductus arteriosus. *Sem Perinatol*, to be published.

66. Coceani F, Bodach E, White EP, et al: 6-keto-PGE_1 is a potent relaxant of the fetal ductus arteriosus. *Prostaglandins*, to be published.

67. Starling MB, Elliott RB: The effects of prostaglandins, prostaglandin inhibitors, and oxygen on the closure of the ductus arteriosus, pulmonary arteries and umbilical vessels in vitro. *Prostaglandins* 8:187-203, 1974.

68. Friedman WF: Studies of the response of the ductus arteriosus, in Heymann MA, Rudolph AM (eds): *The Ductus Arteriosus: Proceedings of the 75th Ross Conference on Pediatric Research.* Columbus, Ohio, Ross Laboratories, 1978, pp 35-43.

69. Olley PM, Coceani F: Use of prostaglandin in the management of cardiopulmonary disease in the neonatal period. *Sem Perinatol*, to be published.

70. Heymann MA, Rudolph AM, Silverman NH: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. *N Engl J Med* 295:530-533, 1976.

71. Merritt TA, Disessa TG, Feldman BH, et al: Closure of the patent ductus arteriosus with ligation and indomethacin: A consecutive experience. *J Pediatr* 93:639-646, 1978.

72. Neal WA, Kyle JM, Mullett MD: Failure of indomethacin therapy to induce closure of patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 91:621-623, 1977.

73. McCarthy JS, Zies LG, Gelband H: Age-dependent closure of the patent ductus arteriosus by indomethacin. *Pediatrics* 62:706-711, 1978.

74. Ivey HH, Kattwinkel J, Park TS, et al: Failure of indomethacin to close persistent ductus arteriosus in infants weighing under 1,000 grams. *Br Heart J* 41:305-307, 1979.

75. Alpert BS, Coceani F, Lewins MJ, et al: Plasma indomethacin levels in pre-term newborn infants with symptomatic patent ductus arteriosus: Clinical and echocardiographic assessments of response. *J Pediatr* 95:578-582, 1979.

76. Kadowitz PJ, Joiner PD, Hyman AL: Physiological and pharmacological roles of prostaglandins. *Am Rev Pharmacol* 15:285-306, 1975.

77. Mathe AA, Hedqvist P, Strandberg K, et al: Aspects of prostaglandin function in the lung. *N Engl J Med* 296:850-855, 910-914, 1977.

78. Tyler T, Leffler C, Wallis R, et al: Effects of prostaglandin of the E-series on pulmonary and systemic circulations of newborn goats during normoxia and hypoxia. *Prostaglandins* 6:963-970, 1975.

79. Kadowitz PJ, Joiner PD, Hyman AL: Effect of prostaglandin E_2 on pulmonary vascular resistance in intact dog, swine and lamb. *Eur J Pharmacol* 31:72-80, 1975.

80. Hyman AL, Kadowitz PJ: Pulmonary vasodilator activity of prostacyclin (PGI_2) in the cat. *Circ Res* 45:404-409, 1979.

81. Lock JE, Coceani F, Olley PM: Pulmonary vascular responses to prostaglandins in the conscious newborn lamb. *Adv Prostaglandin Thromboxane Res*, to be published.

82. Lock JE, Olley PM, Soldin S, et al: Indomethacin-induced pulmonary vasoconstriction in the conscious newborn lamb. *Am J Physiol*, to be published.

83. Lock JE, Olley PM, Coceani F, et al: Use of prostacyclin in persistent fetal circulation. *Lancet* 1:1343, 1979.

84. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G: Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *Br Med J* 1:67-69, 1975.

85. Keirse MJNC: Biosynthesis and metabolism of prostaglandins in the pregnant human uterus. *Adv Prostaglandin Thromboxane Res* 4:87-102, 1978.

86. Goldberg VJ, Ramwell PW: Role of prostaglandins in reproduction. *Physiol Rev* 55:325-351, 1975.

87. Thiery M, Amy JJ: Perinatal effects of natural prostaglandins used for labor induction. *Adv Prostaglandin Thromboxane Res* 4:307-324, 1978.

88. Novy MJ: Effects of indomethacin on labor, fetal oxygenation, and fetal development in rhesus monkeys. *Adv Prostaglandin Thromboxane Res* 4:285-299, 1978.

89. Lewis RB, Schulman JD: Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor. *Lancet* 2:1159-1161, 1973.

90. Wiqvist N, Lundstrom V, Green K: Premature labor and indomethacin. *Prostaglandins* 10:515-526, 1975.

91. Karim SMM: On the use of blockers of prostaglandin synthesis in the control of labor. *Adv Prostaglandin Thromboxane Res* 4:301-306, 1978.

92. Zukerman H, Reiss U, Rubinstein I: Inhibition of human premature labor by indomethacin. *Obstet Gynecol* 44:787-792, 1974.

93. Manchester D, Margolis HS, Sheldon RE: Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn. *Am J Obstet Gynecol* 126:467-469, 1976.

94. Levin DL, Fixler DE, Morriss FC, et al: Morphologic analysis of the pulmonary vascular bed in infants exposed in utero to prostaglandin synthetase inhibitors. *J Pediatr* 92:478-483, 1978.

95. Kloeze J: Relationship between chemical structure and platelet aggregation activity of prostaglandins. *Biochim Biophys Acta* 187:285-292, 1969.

96. Hamburg M, Svensson J, Samuelsson B: Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc Natl Acad Sci USA* 72:2994-2998, 1975.

97. Moncada S, Vane JR: Arachidonic acid metabolites and the interactions between platelets and blood vessel walls. *N Engl J Med* 300:1142-1147, 1979.

98. Roth GJ, Stanford N, Majerus PW: Acetylation of prostaglandin synthetase by aspirin. *Proc Natl Acad Sci USA* 72:3073-3076, 1975.

99. Moncada S, Korbut R: Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. *Lancet* 1:1286-1289, 1978.

100. Burch JW, Baenziger NL, Stanford N, et al: Sensitivity of fatty acid cyclo-oxygenase from human aorta to acetylation by aspirin. *Proc Natl Acad Sci USA* 75:5181-5184, 1978.

101. Malmsten C, Hamberg M, Svensson J, et al: Physiological role of an endoperoxide in human platelets: Hemostatis defect due to platelet cyclo-oxygenase deficiency. *Proc Natl Acad Sci USA* 72:1446-1450, 1975.

102. Willis AL, Comai K, Kahn DC, et al: Dihomo-γ-linoleate suppresses platelet aggregation when administered in vitro or in vivo. *Prostaglandins* 8:509-519, 1974.

103. Majerus PW: Why aspirin? *Circulation* 54:357-359, 1976.

104. Friedman Z, Whitman V, Maisels MJ, et al: Indomethacin deposition and indomethacin induced platelet dysfunction in premature infants. *J Clin Pharmacol* 18:272-279, 1978.

105. Kuo PT, Huang NN, Bassett DR: The fatty acid composition of the serum chylomicrons and adipose tissue of children with cystic fibrosis of the pancreas. *J Pediatr* 60:394-403, 1962.

106. Elliott RB: A therapeutic trial of fatty acid supplementation in cystic fibrosis. *Pediatrics* 57:474-479, 1976.

107. Campbell IM, Crozier DN, Caton RB: Abnormal fatty acid composition and impaired oxygen supply in cystic fibrosis patients. *Pediatrics* 57:480-486, 1976.

108. Chase HP, Dupont J: Abnormal levels of prostaglandins and fatty acids in blood of children with cystic fibrosis. *Lancet* 2:236-238, 1978.

109. Chase HP, Williams RL, Dupont J: Increased prostaglandin synthesis in childhood diabetes mellitus. *J Pediatr* 94:185-189, 1979.

110. Fichman MP, Telfer N, Zia P, et al: Role of prostaglandins in the pathogenesis of Bartter's syndrome. *Am J Med* 60:785-797, 1960.

111. Bowden RE, Gill JR, Radfar N, et al: Prostaglandin synthetase inhibitors in Bartter's syndrome. *JAMA* 239:117-121, 1978.

112. Littlewood JM, Lee MR, Meadow SR: Treatment of Bartter's syndrome in early childhood with prostaglandin synthetase inhibitors. *Arch Dis Child* 53:43-48, 1978.

113. McGiff JC, Wong PYK: Compartmentalization of prostaglandins and prostacyclin within the kidney: Implications for renal function. *Fed Proc* 38:89-93, 1979.

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Indications: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Active immunization against measles (rubeola) in children 15 months of age or older.
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MERUVAX®II (Rubella Virus Vaccine, Live, MSD)—Immunization against rubella (German measles) in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling. May be useful for adolescent and adult males to prevent or control rubella outbreaks in circumscribed population groups. In postpubertal females vaccination must not be undertaken unless the woman is not pregnant, is susceptible to rubella (as shown by Hemagglutination Inhibition test), agrees not to become pregnant for next three months (also in immediate postpartum period), and is informed of frequent occurrence of self-limited arthralgia and possible arthritis beginning two to four weeks after vaccination.
M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles, mumps, and rubella in children 15 months of age to puberty.
M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles (rubeola) and rubella (German measles) in children 15 months of age to puberty.
MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis; therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic and dysgammaglobulinemic states.

Hypersensitivity to Eggs, Chicken, or Chicken Feathers: For measles- and/or mumps-containing vaccines, in patients hypersensitive to eggs, chicken, or chicken feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions.

Pregnancy: *ATTENUVAX*—The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.
Vaccine administration to postpubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of postpubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception that ATTENUVAX, MUMPSVAX, and/or MERUVAX II may be administered simultaneously. BIAVAX II may be administered simultaneously with ATTENUVAX. Monovalent or trivalent poliovirus vaccine, live, oral, may be administered simultaneously with ATTENUVAX and/or MUMPSVAX. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. However, rubella vaccine may be given prior to discharge to susceptible postpartum patients who received blood products, provided that a repeat HI titer is drawn six to eight weeks after vaccination to insure seroconversion; similarly, although rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness, a follow-up postvaccination HI titer should also be determined.
Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines. Vaccination may not result in seroconversion in 100 percent of susceptible subjects.
Measles-Containing Vaccines—Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.
Rubella-Containing Vaccines—Excretion of live attenuated rubella virus from the nose and throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, is not regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.
Measles-Containing Vaccines—Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who previously received killed measles vaccine; the combination vaccines were not given under this condition in clinical trials.
Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5 to 10 cases of SSPE per million cases of natural measles.
Rubella-Containing Vaccines—Adverse reactions include malaise, sore throat, headache, fever, and rash; mild local reactions such as erythema, local pain, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia that is infrequently associated with signs of inflammation, and polyneuritis.
Moderate fever (101–102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.
Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex; being greatest in adult females and least in prepubertal children. In children, joint reactions are rare and of brief duration if they do occur. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3 percent; women: 12–20 percent), and the reactions tend to be more marked and of longer duration. Rarely, symptoms may persist for a matter of months. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (35–45 years), these reactions are generally well tolerated and rarely interfere with normal activities.
Mumps-Containing Vaccines—Parotitis and orchitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2–8 C (35.6–46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2–8 C (35.6–46.4 F), and discard if not used within eight hours. Use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.
Color: The color of the vaccine when reconstituted is yellow. ATTENUVAX is acceptable for use only if clear.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.
BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.
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MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.
Each of these vaccines is supplied as a single-dose vial with a disposable syringe containing diluent and fitted with a 25-gauge, ⅝" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

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Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD;
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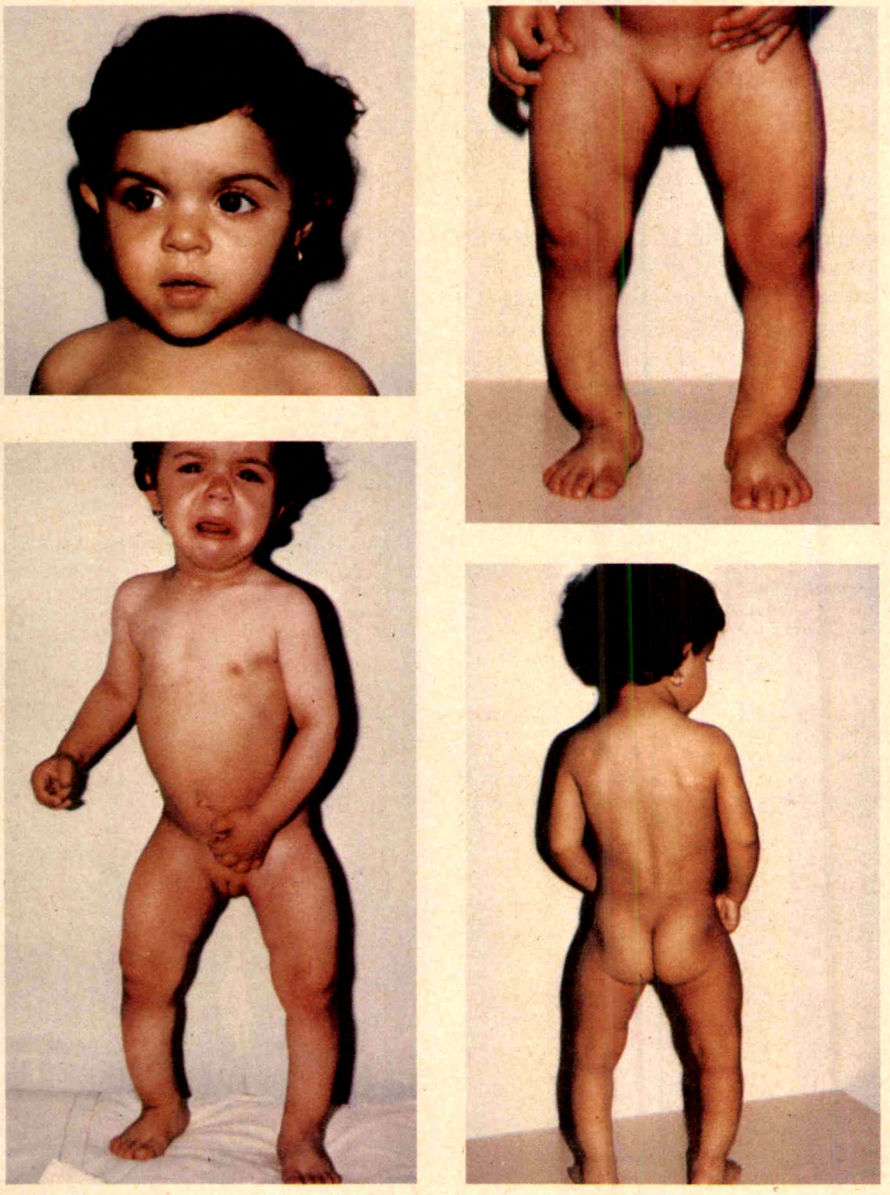

Figure 1.

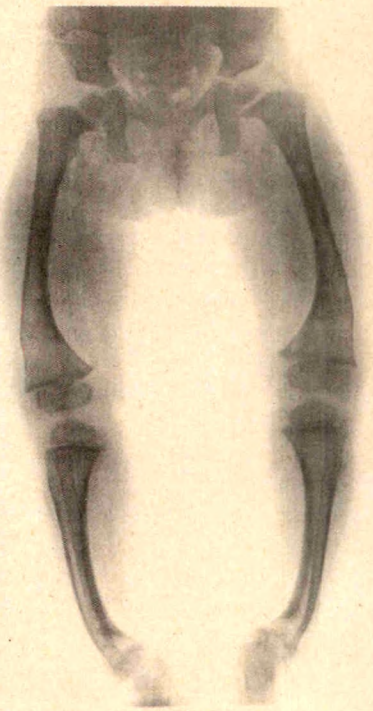

Figure 2.

From the Clinica Pediatricia Universita, Catania, Italy.
Reprint requests to Boston Floating Hospital, 20 Ash St, Boston, MA 02111 (Dr Gellis).

Denouement and Discussion

Metaphyseal Chondrodysplasia, Schmid Type

Fig 1.—Top left, top right, bottom left, bottom right, Short stature, short limbs, and bowed legs.

Fig 2.—Widening and irregularity of metaphysis and coxa vara.

Manifestations

Major clinical manifestations include dwarfism of the short-limbed type, bowed legs, waddling gait, and normal head size. The bowing of the legs is noted prior to ambulation. The head circumference is usually normal. Coxa vara (responsible for the waddling gait) and genu vara are present. Adult height is in the range of 140 cm. Roentgenographic findings consist of widening, cupping, scalping, and irregularity of the metaphysis, which are more marked in the lower limbs, coxa vara, genu vara, and minimal, if any, epiphyseal, diaphyseal and spinal changes. There are other types of metaphyseal chondrodysplasias (eg, Jansen and McCusick types).

Genetics

This type of metaphyseal chondrodysplasia is inherited as an autosomal dominant trait.

Treatment

Treatment consists of orthopedic surgery when indicated, physical therapy, and genetic counseling.

References

1. Dent CE, Normand ICS: Metaphyseal dysostosis type Schmid. *Arch Dis Child* 39:444-454, 1964.
2. Miller SM, Paul LW: Roentgen observations in familial metaphyseal dysostosis. *Radiology* 83:665-673, 1964.
3. Rosenbloom AL, Smith DW: The natural history of metaphyseal dysostosis. *J Pediatr* 66:857-868, 1965.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Radiological Case of the Month

Lionel W. Young, MD; Contributed by MAJ Paul G. Faucher, DO, MC, USA, MAJ A'Delbert Bowen III, MD, MC, USA

A 10-year-old boy was well until ten days prior to admission, when he had intermittent back and neck pain. The pain became more severe and eventually prevented him from getting out of bed. There was no history of trauma. On admission to the hospital, he was in moderate distress, with a straight back and torticollis. Neurological findings were normal and there were no signs of infection. Cervical spine roentgenograms (Fig 1) were obtained.

From the Department of Radiology, Fitzsimons Army Medical Center, Denver.

The opinions contained herein are those of the authors and are not to be construed as the opinions of the Department of the Army or the Department of Defense.

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Figure 1.

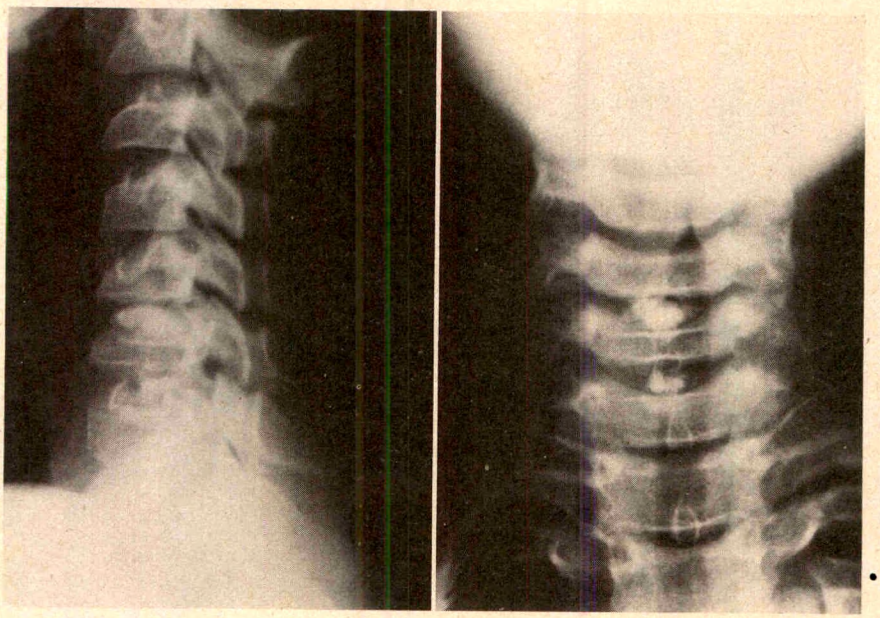


Fig 1.—Calcifications of the nucleus pulposus are present between C-5 and C-6 and between C-6 and C-7. The C-5 and C-6 vertebral bodies are reduced in height.

Fig 2.—Five weeks after initial examination. Note dissolution of calcification from C-6 disk.

Cervical Disk Calcification in Childhood

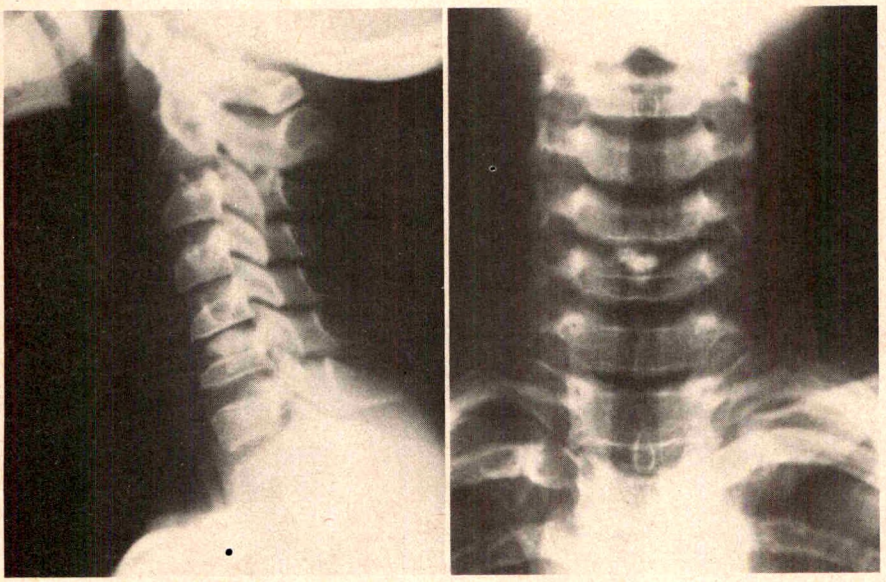
Calcification of the intervertebral disks in childhood is an uncommon but well-described entity occurring preponderantly in boys between 2½ and 11 years of age, the average being 8 years.[1] The cause is unknown although it has occurred in association with congenital cardiac lesions, infection, ruptured intervertebral disks, bilateral cataracts, chalasia, and trauma.[2] The disease is self-limiting. The C-6 disk is the one most commonly affected.[1]

The duration of calcification prior to the onset of symptoms is seldom known because roentgenograms predating symptoms in most instances are not available. The variable course has been gradual disappearance of the calcification during periods from several weeks to years.[1-4] Some observers believe that pain, low-grade fever, leukocytosis, and elevated ESR signal the onset of resorption of the calcification.[5] In the present case, symptoms and signs abated notably after two days of use of a cervical collar and bed rest. On roentgenograms five weeks later, calcification had diminished in the C-5 disk and was no longer visible in the C-6 disk (Fig 2).

In addition to the disk calcification, flattening or wedging of adjacent vertebral bodies has been noted occasionally.[2,3] Anterior or posterior herniation of the calcified disk is a little known complication that may occur in the course of the disease. Spontaneous resorption of the herniated portion of the disk and remission of symptoms after conservative management is the rule.[5] Neurological deficit is rare; one case of transverse myelitis that resolved spontaneously[6] and four cases of neurosurgical intervention[7] for progressive neurological deficit have been reported. Surgery is rarely indicated.[4]

Differential diagnosis includes ochronosis, vitamin D intoxication, and degenerative disk disease. Whereas calcification of the idiopathic variety is centrally located in the nucleus pulposus, calcification in vitamin D intoxication occurs in the annulus fibrosus.[7] Calcifications of degenerative disk disease and ochronosis are usually not manifested until adulthood.

Figure 2.



References

1. Morris J, Niebauer J: Calcification of the cervical intervertebral disc. *Am J Dis Child* 106:295-300, 1963.
2. Melnick JC, Silverman FN: Intervertebral disk calcification in childhood. *Radiology* 80:399-408, 1963.
3. Furukawa K, Hoshino R, Hasue M, et al: Cervical intervertebral-disc calcification in a child: Case report with seven-year follow-up. *J Bone Joint Surg* 59:A692-A693, 1977.
4. Sutton TJ: Calcification of intervertebral discs in childhood. *J Pediatr* 87:1008, 1975.
5. Mainzer F: Herniation of the nucleus pulposus: A rare complication of intervertebral-disk calcification in children. *Radiology* 107:167-170,1973.
6. Newton TH: Cervical intervertebral-disc calcification in children. *J Bone Joint Surg* 40:A107-A113, 1958.
7. Swick HM: Calcification of intervertebral discs in childhood. *J Pediatr* 86:364-369, 1975.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Clinical Memoranda

CSF Eosinophilia During an Acute Coxsackie B4 Viral Meningitis

Eosinophils have been present in the CSF during the course of a variety of parasitic and nonparasitic diseases.[1] To our knowledge, the only viral infection associated with the presence of eosinophils in the CSF has been a chronic meningitis owing to lymphocytic choriomeningitis (LCM) virus in a 2½-year-old child.[1,2] The diagnosis in the patient with LCM viral meningitis was made on the basis of serologic evidence as the virus could not be isolated. We have recently seen an acutely ill child with eosinophils in the ventricular CSF, a CSF pleocytosis, and a coxsackie B4 viral infection documented both serologically and by viral isolation.

Report of a Case.—A 13-month-old male infant was admitted after a prolonged generalized seizure that required ventilatory support. Several hours prior to admission he had a fever, cough, and vomiting. His medical history included the repair of an aortic coarctation at 2 days of age and the insertion of a ventriculoperitoneal (VP) shunt at 3 months of age for porencephaly. His growth and development had been normal. Prior to his admission, he had been receiving digoxin and phenobarbital sodium.

On examination, he was lethargic but had an appropriate response to pain and moved all extremities well. His temperature was 38.3 °C; pulse rate, 138 beats per minute; respiratory rate, 36/min; and blood pressure, 100 mm Hg. He had a discrete maculopapular rash on the lower part of the abdomen and perineum, and his shunt was not obstructed. Other pertinent physical findings included mild nuchal rigidity, a liver edge palpable at 4 to 5 cm below the right costal margin, and a spleen palpable at 3 cm below the left costal margin.

Laboratory investigations disclosed the following values: hemoglobin, 13.3 g/dL; hematocrit, 40%; and WBCs, 10,600/cu mm. The differential cell count was 61% segmented neutrophils, 29% band forms, 7% lymphocytes, 3% mononuclear cells, and the platelet count was 268,000/cu mm. Ventricular CSF obtained through the shunt and examined using Wright's stain had an RBC count of 20/cu mm and a WBC count of 407/cu mm, with 88% mononuclear cells, 11% eosinophils, and 1% segmented neutrophils. The CSF glucose level was 76 mg/dL (4.22 mM/L) with a simultaneous blood glucose level of 107 mg/dL (5.94 mM/L). The CSF protein value was 140 mg/dL. Simultaneous lumbar CSF showed the following values: RBCs, 8,400/cu mm; and WBCs, 6/cu mm, with 4 mononuclear cells and 2 segmented neutrophils. The SGPT value was 10 units/L. Since the diagnostic impression was aseptic meningitis, no antibiotics were given.

Within six hours, his activity and behavior had returned to normal. Although a low-grade fever persisted, all blood and CSF bacterial cultures were negative. He was discharged after 48 hours.

Three weeks later, he was readmitted with a prolonged seizure. No fever, rash, or hepatosplenomegaly were found. The ventricular CSF obtained through the shunt yielded a WBC count of 5/cu mm, three of which were mononuclear cells and two of which were segmented neutrophils. The CSF protein level was 49 mg/dL, and the CSF glucose level was 60 mg/dL (3.33 mM/L), with a simultaneous blood glucose value of 125 mg/dL (6.94 mM/L). No antibiotics were given and all bacterial cultures were negative. Phenytoin sodium was added to his anticonvulsant medications, and since then, he has had no seizures.

During his first admission, a rectal swab yielded coxsackie B4 virus growth, and the complement fixing (CF) titer to that virus was $< 1:8$. A convalescent CF titer obtained during his second admission was 1:256.

Comment.—Eosinophils have been found in the CSF during the course of chronic bacterial, fungal, viral, and helminthic CNS infections.[1-5] They have also been detected during the course of lymphomas and encephalomyelitis and after the injection of foreign proteins into the CSF.[1,2] Three patients who had eosinophils develop in the CSF between 30 and 40 days after the insertion of rubber catheters for ventricular-cisterna magna CSF shunting have also been described.[6,7] The pathogenic importance of eosinophils in the CSF is unclear. In many instances, there has been no peripheral eosinophilia, suggesting that a local hypersensitivity reaction may be responsible.

The patient described here had a silicone elastomer VP shunt inserted ten months prior to his acute coxsackie B4 viral infection. This infection was associated with fever, cough, vomiting, a seizure, rash, and hepatosplenomegaly. A pleocytosis, eosinophils, and an elevated protein level were present in the ventricular CSF, and the lumbar CSF was abnormal in that two segmented neutrophils were present. Three weeks later, he was well, and although the shunt was still present, the ventricular CSF contained only five cells, no eosinophils, and a decreased protein concentration. These findings suggest that the VP shunt was not the cause of the CSF eosinophils.

To our knowledge, the presence of eosinophils in the CSF during an acute viral infection has not previously been reported. Examination of CSF using Wright's or Giemsa's stains, which stain both acidophilic and basophilic cellular structures, should help to determine the incidence of this finding during viral meningitis.

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The Virology Section, Wisconsin State Laboratory of Hygiene, Madison, performed laboratory evaluations of rectal swab and complement fixing titers to coxsackie B4 virus.

1. Kuberski T: Eosinophils in the cerebrospinal fluid. *Ann Intern Med* 91:70-75, 1979.
2. Chesney PJ, Katcher ML, Nelson DB, et al: CSF eosinophilia and chronic lymphocytic choriomeningitis virus meningitis. *J Pediatr* 94:750-757, 1979.
3. Char DFB, Rosen L: Eosinophilic meningitis among children in Hawaii. *J Pediatr* 70:28-35, 1967.
4. Kuberski T, Bart RD, Briley JM, et al: Recovery of *Angiostrongylus cantonensis* from cerebrospinal fluid of a child with eosinophilic meningitis. *J Clin Microbiol* 9:629-631, 1979.
5. Tasker WG, Plotkin SA: Cerebral cysticerosis. *Pediatrics* 63:761-763, 1979.
6. Jeanes AL: Cerebrospinal eosinophilia following Torkildsen's operation. *Guys Hosp Rep* 114:28-31, 1965.
7. Kessler LA, Cheek WR: Eosinophilia of the cerebrospinal fluid of noninfectious origin: Report of two cases. *Neurology* 9:371-374, 1959.

Ebstein's Anomaly of the Tricuspid Valve Associated With Prenatal Exposure to Lithium Carbonate

Congenital malformations have been previously reported in infants born to women who received lithium carbonate during pregnancy.[1] Although this drug has been used in

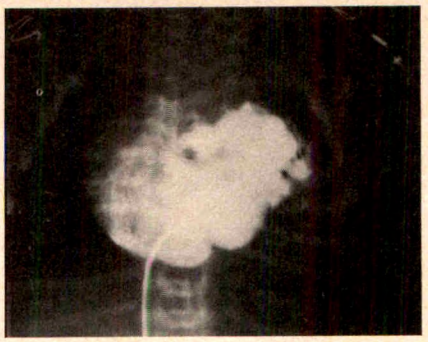
psychiatric therapy since 1949 and has received attention as a possible human teratogen, evidence relative to its teratogenicity on human fetuses is inconclusive. In 1974, Nora et al reported two cases of Ebstein's anomaly of the tricuspid valve in infants whose mothers had received lithium during pregnancy and suggested that the incidence of this rare cardiac defect is strikingly high among such babies.[2] The purpose of our report is to describe another patient in support of the contention that lithium is a potent cardiovascular teratogen.

Report of a Case.—A female infant was delivered at term to a 25-year-old primigravida who had taken 1,200 mg of lithium carbonate daily throughout her entire pregnancy for manic-depressive symptoms. The mother denied taking any other medication during her pregnancy, and there was no known family history of congenital heart disease. At delivery, the baby was noted to have cyanosis, and a heart murmur was heard. Oxygen was administered without demonstrable clinical improvement. The baby was referred to us on the first day of life for further examination.

Physical examination showed a neonate with severe cyanosis who measured 53 cm in length and weighed 4,200 g. The heart rate was 160 beats per minute and the respiratory rate was 60 breaths per minute. The blood pressure by Doppler was 56/24 mm Hg. Peripheral pulses were normal. There was a quadruple rhythm, and a grade 3/6 pansystolic murmur was loudest at the left lower sternal border. The lungs were clear to auscultation. The liver edge was palpable 3 cm below the right costal margin at the midclavicular line. The results of the rest of the physical examination were normal and there was no evidence of additional malformations.

A chest roentgenogram showed a distinctly enlarged heart with diminished pulmonary vascular markings. An ECG showed sinus rhythm with a rate of 140 beats per minute and mean frontal QRS complex axis of +110 degrees. The PR interval was prolonged, with evidence of right atrial enlargement and right ventricular conduction delay. Data from cardiac catheterization and angiocardiography (Figure) were characteristic for Ebstein's anomaly of the tricuspid valve with severe tricuspid valve insufficiency, distinct dilation of the right ventricular outflow tract, and patent ductus arteriosus. She was given digoxin and her condition was clinically improved prior to discharge from the hospital on the fourth day of life.

She has since experienced multiple episodes of paroxysmal supraventricular tachycardia. At 1 year of age she is under close observation while receiving digoxin (Lanoxin) and propranolol hydrochloride (Inderal).



Right ventriculogram shows severe tricuspid valve insufficiency, extreme dilation of right ventricular outflow tract, and "atrialized" right ventricle just to left of spine.

Comment.—The teratogenic effects of lithium have been demonstrated experimentally in many animal species.[3,4] Conclusive evidence for its teratogenicity on the human fetus is lacking. Despite the general consensus that associated congenital malformations in fetuses are probably incidental to treatment with lithium during pregnancy,[5] the Register of Lithium Babies indicates that cardiac malformations have been encountered more frequently than would be expected.[1] Thirteen of 143 infants born to mothers who received lithium during their pregnancy had recognized congenital malformations. Eleven of those infants had cardiovascular defects, including patent ductus arteriosus, mitral atresia, coarctation of the aorta, tricuspid atresia, ventricular septal defect, and Ebstein's anomaly of the tricuspid valve (four cases). In addition, Rane et al reported a case with dextrocardia and coarctation of the aorta.[6] Review of the report of 12 "lithium babies" with cardiovascular anomalies suggests that at least three of the mothers had received no drugs other than lithium. Six of these mothers also received other drugs during their pregnancy, thereby making it difficult to prove that lithium was solely responsible for their infant's cardiovascular malformations. The reported frequency of Ebstein's anomaly is approximately one in 20,000 live births[2]; therefore, it is especially noteworthy that four cases of Ebstein's anomaly have been reported to the Register of Lithium Babies.[1] Nora et al were the first to stress the strikingly high frequency of such a rare defect in "lithium babies," thus implying that this drug can be a potent cardiovascular teratogen in susceptible persons.[2]

Our case had Ebstein's anomaly of the tricuspid valve with documentation that the mother had received no drugs other than lithium during her pregnancy. This case provides additional evidence to support the view that lithium is a potent cardiovascular teratogen. Extreme caution should be exercised to avoid the use of the drug in pregnant or potentially pregnant women.

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Larry Elliott, MD, University of Alabama School of Medicine, Birmingham, gave expert interpretation of the angiocardiograms. Paul Rogers, MD, of Andrews, Tex, referred the patient to us.

Nonproprietary Name and Trademarks of Drug

Lithium carbonate—*Eskalith, Lithane, Lithonate, Lithotabs, PFI-Lithium.*

1. Weinstein MR, Goldfield MD: Cardiovascular malformations with lithium use during pregnancy. *Am J Psychiatry* 132:529-531, 1975.
2. Nora JJ, Nora HA, Toews WH: Lithium, Ebstein's anomaly, and other congenital heart defects. *Lancet* 2:594-595, 1974.
3. Szabo KR: Teratogenic effect of lithium carbonate in the fetal mouse. *Nature* 225:73-75, 1970.
4. Wright TL, Hoffman LH, Davis J: Teratogenic effects of lithium in rats. *Teratology* 4:151-154, 1971.
5. Schardein JL: *Drugs as Teratogens.* Cleveland, CRC Press Inc, 1976, pp 132-133.
6. Rane A, Tomson G, Bjarke B: Effects of maternal lithium therapy in a newborn infant. *J Pediatr* 93:296-297, 1978.

Migration of Inflorescence: Complications of Grass Head Aspiration

Foreign body aspiration may cause acute airway obstruction or chronic and recurrent inflammation of the lung. An unusual aspiration syndrome has been described as following inhalation of the inflorescence, or flower-bearing part, of grasses.[1,2] Structural characteristics of the grass head predispose it to peripheral migration, making spontaneous expectoration unlikely. The length and stiffness of

the spines radiating from the inflorescence dictate its behavior after aspiration. Peripheral migration with airway obstruction characterize timothy grass heads, whereas barley grass heads tend to continue migration through the lung parenchyma and chest wall.

The following case illustrates the complications that may occur after aspiration of a barley grass head. The possibility of foreign body aspiration was not considered in our patient until the inflorescence was found in the pleural cavity.

Report of a Case.—This previously healthy 2½-year-old child had an acute onset of dyspnea and fever. A chest roentgenogram showed a right lower lobe infiltrate, and treatment with oral erythromycin ethylsuccinate was begun. A right pneumothorax was demonstrated the next day when he returned with increasing dyspnea. He was admitted to the local hospital for treatment with parenteral penicillin G potassium. A third chest roentgenogram 24 hours after admission showed a right pleural effusion and therapy was again changed to intravenous methicillin sodium after chest tube placement. A small amount of purulent pleural fluid was obtained and a few Gram-positive cocci were reported on smears stained with Gram's stain. Response to therapy was poor and three days later he was transferred to USAF Medical Center Keesler, Keesler AFB, Miss.

Initial examination revealed a mildly distressed, toxic-appearing child with a temperature of 39.7 °C. Chest roentgenogram at the time of admission showed a large right pleural effusion with a small residual pneumothorax. A tuberculin test was placed, which was nonreactive at 48 hours. Initial WBC count was 27,700/cu mm, with 65 polymorphonuclear leukocytes, eight band forms, 24 lymphocytes, and three mononuclear leukocytes; the hemoglobin level was 8.8 g/dL.

The patient was taken to the operating room, where a right thoracotomy was performed to drain the pleural effusion and place two chest tubes. Cultures of the effusion were obtained for aerobic and anaerobic bacteria, mycobacteria, and fungi. Staining with Gram's stain of the cloudy yellow fluid showed a predominance of small Gram-positive cocci, small Gram-negative rods, and a few larger Gram-negative rods. Broad spectrum antimicrobial treatment was initiated using methicillin sodium, 200 mg/kg/day; gentamicin sulfate, 7.5 mg/kg/day; and chloramphenicol sodium succinate, 100 mg/kg/day.

Temperatures to 40 °C were recorded daily over the next 48 hours. Because of the lack of clinical improvement, a repeat right thoracotomy with extensive decortication of a thick fibrin-pleural peel was accomplished. A foreign body, the stalk and tuft of field grass (Figure), was found in the right pleural cavity overlying the diaphragm. Bronchoscopy was performed and was normal.

Progressive improvement in the patient's condition was observed over the next two weeks while he received antibiotics and chest tube drainage. Pleural fluid cultures grew the following organisms: *Hemophilus segnis*, *Peptococcus* sp, *Bacteroides* sp, and *Peptostreptococcus* sp.

No history suggestive of aspiration could be elicited from the parents. The child has remained healthy over the seven-month follow-up period.

Comment.—The acute onset of respiratory distress, pneumothorax, and pleural effusion in this child suggested aspiration of a foreign body with migration through the lung into the pleural cavity. The organisms isolated from the pleural cavity are common inhabitants of the oral cavity and may have been carried to this site by the grass head.[3] Other sources of a polymicrobic infection of the pleural space were considered, including hepatic and lung abscess. Broad spectrum antimicrobial agents were used, but adequate surgical drainage and removal of the foreign body were required before improvement occurred.

History suggestive of an aspiration episode was not obtained from the parents of this child. Even with a suggestive history, bronchoscopy may be unrevealing because of the rapid peripheral movement of grass heads. Barley grass heads have been found as unexpected inhabitants of chest wall abscesses.[4,5] Migration of the grass head was suggested by Ross to occur through bronchi that allow penetration of the pleura at a right angle with progression into the chest wall.[6] An alternate angle of impact to the pleura may allow intrapleural seeding. The latter course is unusual, as evidenced by the small number of patients reported with intrapleural foreign body. Three children with lung abscess and empyema associated with an intrapleural foreign body have been described.[2,7] Another report described an adult with seven years of pulmonary problems who was found to have an intrapleural barley grass head at the time of thoracotomy.[6]

Timothy grass heads differ from the type found in our patient, in that stiff, radiating spines are lacking. Aspiration of this type of grass head causes an obstructive problem without further migration to the chest wall. Surgical removal of a portion of the lung may be necessary, as the rapid peripheral movement usually precludes bronchoscopic retrieval.[8] The unexpected finding of a grass head in a surgical specimen has also been reported.[9]

Stalk and tuft of field grass found in patient's right pleural cavity overlying the diaphragm at time of operation.

Aspiration of the grass inflorescence is an unusual occurrence. The clinical picture after this type of foreign body aspiration differs from that characteristically associated with other aspiration syndromes. Localized emphysema and atelectasis are unusual, as air will move around and through grass heads.[10] Rapid peripheral migration makes bronchoscopic retrieval less likely, even with repeated attempts. Morbidity after aspiration of obstructive grass heads, such as timothy grass, is related to infection and bronchiectasis. Thoracotomy and pneumonectomy may be required for resolution. Barley grass heads most commonly appear as a chest wall abscess, but may cause serious problems, as illustrated by our patient. Patients with a history of grass head aspiration and negative bronchoscopy may require thoracotomy to prevent these complications.

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The views expressed herein are those of the authors and do not necessarily reflect the views of the US Air Force or the Department of Defense.

Nonproprietary Name and Trademark of Drug

Gentamicin sulfate—*Garamycin.*

1. Jackson C: Grasses as foreign bodies in the bronchus and lung. *Laryngoscope* 62:897-923, 1952.
2. Clery A, Ellis F, Schmidt H: Problems associated with aspiration of grass heads (inflorescences). *JAMA* 171:1478-1484, 1959.
3. Kilian M: A taxonomic study of the genus *Haemophilus*, with the proposal of a new species. *J Gen Microbiol* 93:9-62, 1976.
4. Sehring M, Shaw E: The passage of a foreign body (foxtail) through the bronchus, lung, pleura and thoracic wall. *Pediatrics* 1:210-213, 1948.
5. Cavens T, McGee M, Miller R, et al: Pneumocutaneous fistula secondary to aspiration of grass. *J Pediatr* 82:737-738, 1973.
6. Ross D: Inhaled intrapleural foreign body. *Br J Surg* 41:412-414, 1954.
7. Seydell E: Spontaneous perforation of the wall of the chest by an aspirated foreign body. *Arch Otolaryngol* 26:189-194, 1937.
8. Carter M, Welch K: Bronchiectasis following aspiration of timothy grass. *N Engl J Med* 238:832-836, 1948.
9. Jewett T, Butsch W: Trials with treacherous timothy grass. *J Thorac Cardiovasc Surg* 50:124-126, 1965.
10. Woolley P: Grass inflorescences as foreign bodies in the respiratory tract. *J Pediatr* 46:704-706, 1955.

Spinal Cord Compression: An Unusual Manifestation of Pseudohypoparathyroidism

Pseudohypoparathyroidism is a disorder characterized by typical somatic features, hypocalcemia, hyperphosphatemia, elevated circulating levels of parathormone (PTH), and unresponsiveness to parathyroid injection.[1,2] Although the clinical and roentgenographic features of this condition have been the subject of various reports and reviews,[1,3] abnormalities of the spine are rarely described. In this report, we present a patient with pseudohypoparathyroidism who had spinal cord compression owing to bony narrowing of the spinal canal.

Report of a Case.—A 3-year 10-month-old boy was evaluated for short stature and developmental delay. His birth history and medical history were unremarkable. There was no history of seizures or tetany. The mother was found to have pseudo-pseudohypoparathyroidism based on clinical and biochemical features and confirmed by normal urinary adenosine 3′:5′-cyclic phosphate (cAMP) response to parathyroid injection.[2] He was short (height age, 1 year and 10 months) and obese, and he had rounded facies and small and broad hands with stubby fingers. Severe psychomotor retardation was noted. His strength, muscle tone, and deep-tendon reflexes were normal. The serum calcium level was 8 mg/dL; phosphorus, 7.9 mg/dL; PTH, 285 μLEq/mL (normal, 0 to 10 μLEq/mL). An intravenous infusion of 200 μ of bovine parathyroid injection failed to increase the urinary excretion of phosphate and of cAMP.

Roentgenographic studies of the skull indicated no intracranial calcifications; the basal angle of Welcker was 143 °, indicating platybasia[4]; films of the pelvis showed mild bilateral coxa valga; hand films showed decreased bone density, coarse trabeculation, short metacarpals, and short phalanges. The bone age of 5 years was substantially advanced. He was treated with dihydrotachysterol, but compliance was poor, and he had persistent hypocalcemia (7.3 to 8 mg/dL) and hyperphosphatemia (7.9 to 8.5 mg/dL) during the following months.

At 4½ years, he was admitted to the hospital for evaluation of progressive decline of motor functions, which had begun two months previously with difficulty in moving his arms. Subsequently, there was gradual loss of his ability to walk, stand, and sit unsupported. He had no change in bladder or bowel function. There was no history of trauma or febrile illness. Neurological examination revealed intact cranial nerves and severe quadriparesis. His serum calcium level was 8.0 mg/dL and serum phosphorus value was 5.1 mg/dL. Roentgenograms of the spine showed a striking reduction in the sagittal diameter of the spinal canal at the level of C-3 and C-4, which measured, respectively, 9.5 mm and 10 mm[5] (Figure). Narrowing of the canal was also evident in the lumbar region, with severe reduction of the interpediculate distances, ranging from 15.5 mm at the level of L-5 to 17 mm at L-1.[6] Osteoporosis was not present. A myelogram depicted a narrow thecal sac in the lumbar and cervical regions, with nearly complete block from the C-2 to C-6 levels.

The patient underwent laminectomy from C-2 to C-5; the dura was tense and bulging, with pulsation returning after decompression. There was partial recovery of motor function after surgery. Thus, one year later, he uses his arms to feed himself, is able to sit briefly unsupported, but has severe spasticity of the lower extremities.

Lateral view of cervical spine. Notice reduction of sagittal diameter of cervical canal, more striking (arrows) at C-3 (9.5 mm) and C-4 (10 mm).

Comment.—In 1942, Albright et al described a syndrome of a characteristic phenotype, clinical signs of hypoparathyroidism and evidence of peripheral resistance to parathyroid extract.[1] Subsequently, Chase et al observed that patients with pseudohypoparathyroidism have a lack of or defective PTH-sensitive adenyl cyclase in renal tissue, and they assumed that the metabolic defect in bone would be of a similar nature.[2] Drezner et al, however, suggested that the hypocalcemia and the bone disease in this condition are due to a state of vitamin D deficiency, resulting from inability of the kidney to convert 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol.[7] Nevertheless, the basic osseous abnormalities in pseudohypoparathyroidism are distinct from those encountered in other states of vitamin D deficiency and seem to be genetically determined. Most frequently, they include thickened calvaria, shortening of the metacarpals, coxa valga, exostoses, and advanced bone maturation.[3] Our patient had several of these typical changes, in addition to which severe abnormalities in the skull and spine were present. To our knowledge, platybasia has not been reported in association with pseudohypoparathyroidism, and its occurrence, in our patient, remains unexplained. Roentgenographic changes of the spine are seldom described. Decreased sagittal diameter of the lumbar vertebral canal has been previously described in a patient with this condition,[8] and Cullen and Pearce have described spinal cord compression in a patient who

was found to have excessive bone formation inside the vertebral canal.[9] Spinal cord compression owing to bone overgrowth has also been noted by Highman et al in adult patients with vitamin D-resistant osteomalacia.[10] These authors speculated that treatment with vitamin D or dihydrotachysterol may have stimulated further bone deposition and caused compression of the cord in a spinal canal already narrowed by the basic process. Likewise, it is possible that treatment with dihydrotachysterol in our patient aggravated preexisting abnormalities of the spinal canal, or that therapy may have been solely responsible for those changes. Alternatively, we believe that the bony thickening of the spinal canal may, in fact, be part of the osseous changes that are genetically determined in pseudohypoparathyroidism.

Structural changes of the spine in pseudohypoparathyroidism may be more common than currently appreciated. The findings from our patient probably represent the severe end of a spectrum of osseous changes not yet explored in detail. Roentgenographic studies of the skull and spine and careful neurological examinations should be considered in the assessment and follow-up of patients with this condition.

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1. Albright F, Burnett CH, Smith PH, et al: Pseudohypoparathyroidism: An example of 'Seabright bantam syndrome.' *Endocrinology* 30:922-932, 1942.

2. Chase LR, Melson GL, Aurbach GD: Pseudohypoparathyroidism: Defective excretion of 3',5'-AMP in response to parathyroid hormone. *J Clin Invest* 48:1832-1844, 1969.

3. Steinbach HL, Young DA: The roentgen appearance of pseudohypoparathyroidism (PH) and pseudo-pseudohypoparathyroidism (PPH). *Am J Roentgenol* 97:49-66, 1966.

4. Taveras JM, Wood EH: *Diagnostic Neuroradiology*, ed 2. Section 1: *Golden's Diagnostic Radiology;* LL Robbins (section ed). Baltimore, Williams & Wilkins Co, 1976, pp 51-60.

5. Hinck VC, Hopkins CE, Savara BS: Sagittal diameter of the cervical spinal canal in children. *Radiology* 79:97-108, 1962.

6. Hinck VC, Clark WM, Hopkins CE: Normal interpediculate distances (minimum and maximum) in children and adults. *Am J Roentgenol* 97:141-153, 1966.

7. Drezner MK, Neelon FA, Haussler M, et al: 1,25-Dihydroxycholecalciferol deficiency: The probable cause of hypocalcemia and metabolic bone disease in pseudohypoparathyroidism. *J Clin Endocrinol Metab* 42:621-628, 1976.

8. Ablow RC, Hsia YE, Brandt IK: Acrodysostosis coinciding with pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism. *Am J Roentgenol* 128:95-99, 1977.

9. Cullen DR, Pearce JM: Spinal cord compression in pseudohypoparathyroidism. *J Neurol Neurosurg Psychiatry* 27:459-462, 1964.

10. Highman JH, Sanderson PH, Sutcliffe MML: Vitamin D resistant osteomalacia as a cause of cord compression. *Q J Med* 156:529-537, 1970.

Complications of Propranolol Use in Neonatal Thyrotoxicosis

Neonatal thyrotoxicosis presents a difficult management problem. Recent reports have proposed that neonatal thyrotoxicosis may be effectively and safely treated with propranolol hydrochloride alone.[1,2] Smith and Howard's report emphasized that their patient did not show clinical improvement while receiving iodides, thioamides, and phenobarbital until the addition of propranolol.[3] A recent article has suggested that "beta blockade should be the treatment of choice for neonatal thyrotoxicosis."[4] However, we would like to report a case in which propranolol used alone for this purpose caused episodic bradycardia without otherwise improving the patient's clinical status.

Report of a Case.—The patient was a 2,170-g female infant born at 37 weeks' gestation to a 22-year-old multigravida referred to the St Paul (Minn) Ramsey Perinatal Center. One year prior to delivery, the infant's mother had been treated with radioactive iodine for hyperthyroidism. She received 50 μg daily of levothyroxine sodium (Synthroid Tabs) during this pregnancy. At birth, the infant was small for gestational age and had a head circumference of 29.5 cm. No other abnormalities were noted. At 20 hours of age, the infant became jittery, tachypneic, and tachycardiac. Phenobarbital sodium therapy was initially begun because of concern of possible drug withdrawal. No evidence of drug withdrawal was subsequently found. Bacterial cultures were obtained and were negative.

At 36 hours of age, the infant had loose, yellow stools occurring ten to 15 times per day. Beginning at 3 days of age, she displayed a voracious appetite, consuming more than 200 calories per kilogram per day. But by the fifth day of life, she weighed 110 g less than her birth weight. At 5 days of age, the serum T_4 value (radioimmunoassay) was greater than 24.5 μg/dL. Reexamination at this time disclosed a jittery, plethoric, small infant. Heart rate varied between 130 to 200 beats per minute; respiratory rate was 60 to 70/min. The infant's axillary temperature intermittently increased to 37.5 °C. The eyelids were slightly puffy, but there was no exophthalmos. Thyroid tissue was palpable just above the sternal notch. There was no evidence of congestive heart failure.

Therapy with propranolol hydrochloride, 2 mg orally every 12 hours, was begun. Phenobarbital therapy was stopped. Twenty-four hours later, propranolol hydrochloride was increased to 2 mg every eight hours. With the increase in the dosage of the drug, episodes lasting 10 to 15 s of heart rates between 80 to 90 beats per minute (sinus bradycardia by ECG) were noted. These episodes were most frequent two to four hours after propranolol administration. Between these episodes, the heart rate was 120 to 170 beats per minute. Despite the episodic bradycardia, the infant's status otherwise was unchanged.

At 8 days of age, propylthiouracil, 4 mg every eight hours, and strong iodine solution (Lugol's solution), one drop every eight hours, were added to the regimen. Three days later, the infant started to gain weight, had less diarrhea, and was less irritable. Frequent episodes of sinus bradycardia continued, however, and at 14 days of age, the propranolol therapy was discontinued. The serum T_4 value at this time was 14.2 μg/dL. Thereafter, the heart rate was consistently greater than 120 beats per minute. The infant continued to show improvement and was discharged at 3 weeks of age on a regimen of propylthiouracil and strong iodine solution. Propylthiouracil therapy was continued for six months. At 8 months of age, the infant is no longer receiving any medication, and she is clinically and chemically euthyroid. She is growing along the fifth percentile, and she is showing age-appropriate development.

Comment.—Propranolol may control the signs and symptoms of hyperthyroidism, and it has been successfully used in the treatment of neonatal hyperthyroidism. For these reasons, we elected to treat our patient with this drug. Unlike other reported cases, however, our patient did not show rapid clinical improvement. Bradycardia occurred several times each day, and this undesirable effect did not abate until propranolol therapy was stopped. Only with the addition of iodides and propylthiouracil to the regimen did the baby's symptoms of irritability, diarrhea, weight loss,

tachypnea, and tachycardia show improvement.

Propranolol, a β-adrenergic antagonist, has many pharmacological effects. Pulse rate seems to be especially sensitive to the action of this drug. Negative chronotropic changes in normal adults given propranolol are more profound and long lasting than are inotropic changes.[5,6] Sensitivity of heart rate to this drug is also apparent in thyrotoxicosis. Mazzaferri et al treated hyperthyroid adults with propranolol alone and noted no difference in pulse rate between them and euthyroid controls.[7] However, other evidence of hyperthyroidism was still apparent in most of their patients. Other studies have confirmed that although pulse rate may be normalized or palpitations may be controlled with propranolol, other signs and symptoms of hypermetabolism may continue.[8-10]

Our patient's intermittently slow heart rate with evidence of otherwise inadequate β-blockade probably represents another example of the disparity between the chronotropic action of propranolol and its other effects. The possibility that this infant had an idiosyncratic response to the drug cannot be excluded.

In mild cases of neonatal hyperthyroidism (as manifested only by tachycardia), small doses of propranolol might be appropriate. In infants who are more seriously ill, other drugs may have to be used to ensure a satisfactory clinical response. In these instances, propranolol should not be considered the only drug of choice. Administration of propranolol, whether used alone or in conjunction with other therapeutic agents, makes continuous cardiac monitoring mandatory.

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1. Pemberton PJ, McConnell B, Shanks RG: Neonatal thyrotoxicosis treated with propranolol. *Arch Dis Child* 49:813-815, 1974.
2. Pearl KN, Chambers TL: Propranolol treatment of thyrotoxicosis in a premature infant. *Br Med J* 2:738, 1977.
3. Smith CS, Howard NJ: Propranolol in treatment of neonatal thyrotoxicosis. *J Pediatr* 83:1046-1048, 1973.
4. Oski FA, Stockman JA (eds): *1979 Yearbook of Pediatrics*. Chicago, Year Book Medical Publishers, 1979, pp 290-291.
5. Robinson JL, Rich JM, Weissler AM, et al: Differential effects of propranolol on the chronotropic and inotropic response to isoproterenol in man. *Am J Cardiol* 31:155, 1973.
6. Boudoulas H, Beaver BM, Kates RE, et al: Pharmacodynamics of inotropic and chronotropic responses to oral therapy with propranolol. *Chest* 73:146-153, 1978.
7. Mazzaferri EL, Reynolds JC, Young RL, et al: Propranolol as primary therapy for thyrotoxicosis. *Arch Intern Med* 136:50-56, 1976.
8. Pimstone B, Joffe B, Pimstone N, et al: Clinical response to long-term propranolol therapy in hyperthyroidism. *S Afr Med J* 43:1203-1205, 1969.
9. McLarty DG, Brownlie FEW, Alexander WD, et al: Remission of thyrotoxicosis during treatment with propranolol. *Br Med J* 2:332-334, 1973.
10. Eriksson M, Rubenfeld S, Garber AJ, et al: Propranolol does not prevent thyroid storm. *N Engl J Med* 296:263-264, 1977.

Diphtheroid Sepsis in a Child With No Predisposing Condition

Diphtheroids – *Corynebacterium* species other than *C diphtheriae*–are ubiquitous organisms and rarely pathogenic. When isolated in cultures of blood and other usually sterile body sites, diphtheroids are commonly dismissed as contaminants.[1] In 1978, diphtheroids accounted for 3.2% of positive blood cultures and grew from 0.2% of all blood cultures (4,000) at the Montreal Children's Hospital (MCH).

A child, recently hospitalized at the MCH for evaluation of fever of unknown origin, was discharged without a diagnosis. The growth of diphtheroids in two of seven blood cultures was dismissed as unimportant because the child did not seem to be a compromised host and no apparent nidus of infection could be found. Subsequent events proved that these diphtheroids were the cause of his illness. The purpose of this report is to encourage the critical evaluation of *all* isolates from normally sterile sites such as blood, CSF, and bone marrow.

Report of a Case.–An 8½-year-old boy was admitted to the MCH to evaluate a fever of ten days' duration, accompanied by a frontal headache, malaise, anorexia, and irritability. The past medical history and review of systems as well as detailed travel, contact, and environmental histories were unremarkable. On admission, he was pale, thin, irritable, and had a temperature of 39 °C. The only abnormal physical findings were a grade 1-2/6 nonradiating systolic ejection murmur over the pulmonic valve area, sustained ankle clonus, and hyperreflexia of the knee and ankle.

By day 3 of hospitalization, the results of the neurological examination had become normal and the murmur had been assessed as physiologic by the cardiologists. The patient, however, remained febrile and irritable. Blood cultures were collected almost daily while the following laboratory data were obtained: a hemoglobin concentration of 9.8 g/dL; a peripheral WBC count of 9,100/cu mm, with 80% neutrophils and 5% band forms; a normal number of platelets; and an ESR of 64 mm/hr. Lumbar CSF was normal except for the presence of seven WBCs per cubic millimeter, two of which were neutrophils. Results of urinalysis, blood chemistries, immunoglobulin levels, C3, and C4 were all normal. Tests for rheumatoid factor and antinuclear antibody screening test to detect presence of antibodies of five different types of streptococci (streptozyme), slide test for heterophil antibody of infectious mononucleosis, and tests for agglutinins for *Salmonella*, *Brucella*, and tularemia were all negative. Repeated bacterial, viral, and fungal cultures of the urine, throat, and stool did not indicate pathogens. Tuberculin skin tests were negative. Roentgenograms of his chest, sinuses, skull, and gastrointestinal tract, as well as computerized tomography of his head, total body scan using gallium citrate Ga 67, abdominal ultrasound examination, and serial echocardiograms and ECGs were all normal. A bone marrow biopsy specimen showed normal histologic findings.

On day 13 of hospitalization, two sets of blood cultures, drawn 12 hours apart from different sites four days earlier, contained diphtheroids. Subsequent blood cultures were sterile, and the diphtheroids were dismissed as contaminants. On day 18, the patient was discharged shortly before diphtheroids were noted growing from the bone marrow aspirate obtained on day 11.

On examination four days after discharge, the patient was febrile, looked ill, and was found to have left-sided hyperreflexia. The patient was readmitted to the hospital and erythromycin lactobionate therapy was started for presumed diphtheroid endocarditis. (Erythromycin was selected based on the sensitivity patterns of other MCH diphtheroid isolates.) Three days later, because of continuing neurological symptoms and fever, another lumbar puncture was done. The CSF showed diphtheroid growth, whereas a skin swab from the prepared lumbar puncture site was sterile. The only other abnormal finding in the CSF was a protein concentration of 42 mg/dL.

Minimal inhibitory concentrations (MICs) of erythromycin, penicillin G potassium and gentamicin sulfate against the bone marrow and CSF isolates were 128 μg/mL, 0.12 μg/mL, and 0.003 μg/mL. Because of the duration and severity of the patient's illness, combination antimicrobic therapy with penicillin G potassium and gentamicin was begun. Our laboratory, as

well as the Laboratory Center for Disease Control, Ottawa, Ontario, Canada, was unable to further speciate the corynebacteria isolates.

Three days after beginning the appropriate antimicrobics, the patient was afebrile, hungry, and generally feeling well. Repeated CSF and blood cultures were sterile. After 18 days of combined parenteral antimicrobic therapy, the patient was given oral potassium phenoxymethyl penicillin therapy alone, which was continued for five weeks. Although his hemoglobin concentration rapidly returned to normal, his ESR remained elevated for six weeks. By four weeks after discharge from the hospital, the patient had gained more than 3 kg. He continues to be entirely well.

Comment.—Corynebacteria are Gram-positive, nonmotile, catalase-positive, pleomorphic bacilli that are commonly present on normal human skin and mucous membranes and that are part of the normal intestinal flora.[1] Diphtheroids—corynebacteria other than *C diphtheriae*—are generally considered to be nonpathogenic in man. Diphtheroids are not only common contaminants of clinical specimens, but they also are frequently fastidious and slow growing, requiring prolonged incubation.[1] Once the organism is isolated, further speciation may not always be possible, as in this case.

Reports of diphtheroid infections in children generally describe patients with anatomic abnormalities of the heart or CNS or patients after surgery or trauma. The most frequent infections are bacterial endocarditis,[1-3] acute meningitis,[1,2,4] and CSF shunt infections.[2,5,6] Acute meningitis[4] and endocarditis[1-3] have also occasionally been reported in normal children.

Although reports of diphtheroid sepsis are not unusual in adults with malignant neoplasms, diphtheroids are not being reported as a cause of sepsis in similarly compromised children.[1,2,6-8] In a recent review of septicemia in children with acute leukemia, 20% of the blood isolates were either *Staphylococcus albus* or *Propionibacterium acnes* (a diphtheroid).[9] For reasons not stated by the authors, these organisms were excluded from analysis.

The purpose of this report is to emphasize that "nonpathogens" such as diphtheroids can cause serious infections in children. The problem for the clinician is to decide when these organisms are causing disease. The most critical element in making such a diagnosis is a high index of suspicion. Children with congenital abnormalities of the heart or CNS or those receiving immunosuppressive therapy seem to be at highest risk. The situations that should make one wary include the isolation of the same organism from more than one site that is usually sterile, such as blood and CSF, or the isolation of the organism from the same source on repeated occasions.

Meticulously sterile technique during culture collection is also important. In cases where repeated cultures are being collected because previous specimens contained "contaminants," it is useful to culture the prepared site at the same time as the new specimen is obtained.

The laboratory also can be of assistance in evaluating culture results. Although infrequently done, pour-plate cultures, in which 1 mL of blood is added to 15 mL of melted nutrient agar, may be helpful. One or two colonies per milliliter of blood suggests contamination, whereas multiple colonies usually represent bacteremia.[10]

Similarly, if a diphtheroid isolate is considered to be a pathogen, the laboratory can do specific sensitivity testing. This is important since there are wide strain-to-strain variations in antimicrobic sensitivities.[1] If the patient's condition dictates therapy before sensitivities are known, empirical treatment with a penicillin and a chloramphenicol is suggested as many diphtheroids are sensitive to one or both.[1,2,5] However, definitive treatment must be based on the MICs-minimum bacteriocidal concentrations of antimicrobic agents for the isolate.

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Nonproprietary Name and Trademark of Drug

Gentamicin sulfate—*Garamycin.*

1. Johnson WD, Kaye D: Serious infections caused by diphtheroids. *Ann NY Acad Sci* 174:568-576, 1970.
2. Kaplan K, Weinstein L: Diphtheroid infections in man. *Ann Intern Med* 70:919-929, 1969.
3. Merzbach D, Freundlich E, Metzker A, et al: Bacterial endocarditis due to *Corynebacterium. J Pediatr* 67:792-796, 1965.
4. French RS, Ziter FA, Spruance SL, et al: Chronic meningitis caused by *Propionibacterium acnes. Neurology* 24:624-628, 1974.
5. Everett ED, Eickhoff TC, Simon RH: Cerebrospinal fluid shunt infections with anaerobic diphtheroids (*Propionibacterium* species). *J Neurosurg* 44:580-584, 1976.
6. Hande KR, Witebsky FG, Brown MS, et al: Sepsis with a new species of *Corynebacterium. Ann Intern Med* 85:423-426, 1976.
7. Carpenter JL, Blom J: *Corynebacterium equi* pneumonia in a patient with Hodgkin's disease. *Am Rev Respir Dis* 114:235-239, 1976.
8. Pearson TA, Braine HG, Rathburn HK: *Corynebacterium* sepsis in oncology patients. *JAMA* 238:1737-1740, 1977.
9. Chilcote RR, Baehner RL: Septicemia in association with acute lymphoblastic leukemia. *J Pediatr* 94:715-718, 1979.
10. MacGregor RR, Beaty HN: Evaluation of positive blood cultures. *Arch Intern Med* 130:84-87, 1972.

Focal Cerebral Atrophy in Incontinentia Pigmenti Achromians

Incontinentia pigmenti achromians (IPA), also called hypomelanosis of Ito, is an uncommon cutaneous anomaly. Abnormalities in other organs, including the brain, have been found in about 50% of the patients so far reported.[1,2] Focal, as opposed to generalized, neurological symptoms have rarely been described although previous reports have been limited to the dermatological literature and neurological investigations have not been adequate to establish the nature of the brain lesions. This is a description of a patient with IPA who had focal cerebral atrophy.

Report of a Case.—A 13-year-old black boy was referred for neurological evaluation because of the recent onset of seizures. He had been born at full term after an uneventful pregnancy and delivery. The neonatal period was complicated by jaundice and a blood transfusion. At 4 months of age, his mother noticed an irregular area of hypopigmentation on the right thigh, which extended during the next several years to the right hip and buttock. Early developmental landmarks were normal, but since beginning grade school, he had attended special education classes.

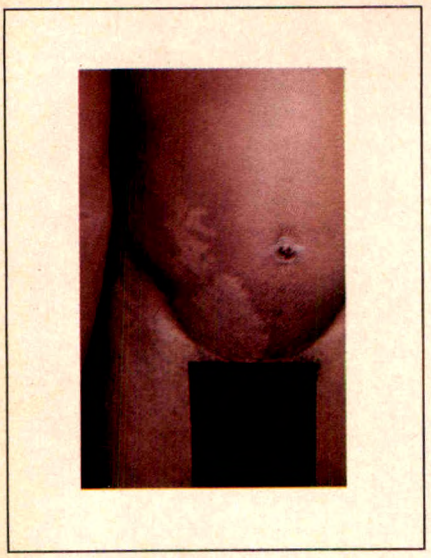

Fig 1.—Irregular, patchy areas of hypopigmentation over patient's right lower side of abdomen and thigh are characteristic of incontinentia pigmenti achromians.

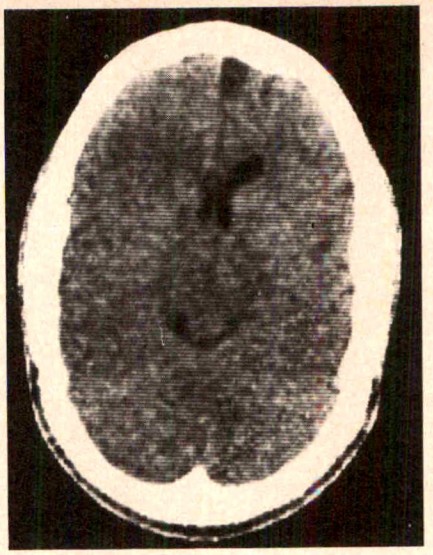

Fig 2.—Dilated frontal horn of left lateral ventricle and widened sulci on computerized tomographic brain scan indicate left frontal atrophy.

Six months before evaluation, he started to have seizures once or twice each month. These consisted of staring and clonic jerking of the right hand that then became generalized. There was no history of seizures, mental retardation, or skin lesions in his family, who included one younger sister and one younger brother.

On dermatological examination, there was unilateral patchy and speckled hypopigmentation extending from the umbilical area over the lower part of the abdomen to the buttock and the right thigh (Fig 1). Wood's lamp examination indicated no other changes. The rest of the results of the general medical examination, including dentition, were normal.

On neurological examination, he missed double simultaneous stimulation on the right hand and face, but other tests of parietal sensation and the rest of the neurological examination showed no abnormalities. Neuro-ophthalmological examination results, including those for visual acuity, fields, and funduscopic examination, were normal.

Biopsy specimens were taken of hypopigmented and normal skin. Hematoxylin-eosin and Fontana-Masson stains were performed, and frozen sections were studied by the dopa technique. In the specimen of hypopigmented skin, the amount of melanin was decreased and the dopa reaction was weaker in the basal layer of the epidermis. There was no incontinence of melanin granules into the dermis, and no inflammation. Electron microscopy showed a reduction in the number of melanosomes in the basal melanocytes.

Psychometric testing included the Wechsler Intelligence Scale for Children-Revised, Halstead-Reitan neuropsychological test battery, Wechsler Memory Test, and the Aphasia Screening Test. Full-scale IQ was 54 (verbal IQ, 58; performance IQ, 58). There was a prevalence of errors in the processing of language and language symbols.

The EEG demonstrated focal spike discharges in the left temporal and parietal head regions, with associated persistent focal polymorphic delta activity. Computerized tomographic (CT) brain scan demonstrated left frontal atrophy (Fig 2). The CSF and the skull roentgenograms were normal.

The patient's seizures were controlled by phenobarbital sodium and phenytoin sodium. Results of follow-up dermatological and neurological examinations, skin biopsy specimen, psychometrics, EEG, and CT scan performed one year later were unchanged.

Comment.—The diagnosis of IPA is based on the characteristically irregular, swirling hypopigmentation found on clinical examination. This may affect any part of the body, unilaterally or bilaterally. Decreased melanin in the basal epidermis is confirmed by dopa reaction and electron microscopy. In contrast to incontinentia pigmenti, which it resembles, preceding inflammation of the skin does not occur. The disorder is usually not familial.

Abnormalities in other organs, usually the skeleton, eye, and brain, are common. The most common skeletal problems are scoliosis or limb asymmetry. Eye involvement most frequently includes strabismus, choroidal atrophy, or retinal pigmentary changes.[1,2]

One fourth of patients with IPA have mental retardation or seizures, often coexisting in the same patient.[1,2] Other neurological abnormalities, including macrocrania and hypotonia, have been reported.[2-4] Our patient had symptoms and signs of left cerebral hemisphere dysfunction, including language impairment, parietal sensory deficit, focal seizures, and focal abnormalities on the EEG and the CT brain scan. The hypopigmentation of his skin was limited to the right side of the body. With the exception of our patient, focal neurological findings have been mentioned in only two patients, neither studied in detail. Both patients had focal abnormalities on EEG, one with ipsilateral skin lesions[5] and the other with contralateral skin lesions.[4]

This report demonstrates that, in contrast to the Sturge-Weber and linear nevus sebaceous syndromes, focal cutaneous and cerebral abnormalities are not inevitably ipsilateral in IPA. Detailed evaluations of future patients, including CT brain scans, are needed to determine the true frequency and importance of focal neurological lesions in patients with IPA.

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1. Cram DL, Fukuyama K: Unilateral systematized hypochromic nevus. *Arch Dermatol* 109:416, 1974.

2. Grosshans EM, Stoebner P, Bergoend H, et al: Incontinentia pigmenti achromians (Ito). *Dermatologica* 142:65-78, 1971.

3. Jelinek JE, Bart RS, Schiff GM: Hypomelanosis of Ito ('incontinentia pigmenti achromians'): Report of three cases and review of the literature. *Arch Dermatol* 107:596-601, 1973.

4. Peña L, Ruiz-Maldonado R, Tamayo L, et al: Incontinentia pigmenti achromians (Ito's hypomelanosis). *Int J Dermatol* 16:194-202, 1977.

5. Schwartz MF Jr, Esterly NB, Fretzin DF, et al: Hypomelanosis of Ito (incontinentia pigmenti achromians): A neurocutaneous syndrome. *J Pediatr* 90:236-240, 1977.

Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

Injuries and Child Abuse

Sir.—I was encouraged to see in the JOURNAL (133:906-909, 1979) another article (this by Ellerstein) describing the superficial injuries of abused and neglected children. Minor injuries are more common in this population[1] than major injuries and may antecede them.[2] We have recently published data[3] that expand on Dr Ellerstein's statement, "Multiple bruises of the buttocks or the genital area are not commonly accidental."

Compared to two groups of accidentally injured children, soft-tissue injuries (contusions, abrasions, scratches, and lacerations) were more common in the abused group ($P < .001$) not only over the buttocks and genitalia, but also over the cheeks, neck, trunk, and posterior thigh. Lacerations were almost seven times more common in the accidently injured emergency room group than in the abused group ($P < .001$). Dr Ellerstein's focus on superficial injuries is helpful but his failure to emphasize their distribution "neglects" a useful cue in the diagnosis of child abuse.

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1. Vincent F (ed): *Study of Child Neglect and Abuse Reporting for 1975 by the American Humane Association.* No. (OHD) 77-30086, Department of Health and Human Services, 1977.

2. O'Neill JA Jr, Mecham WF, Griffin PP, et al: Patterns of injury in the battered child syndrome. *J Trauma* 13:332-339, 1973.

3. Pascoe JM, Hildebrandt HM, Tarrier A: Patterns of skin injury in nonaccidental and accidental injury. *Pediatrics* 64:245-247, 1979.

Streptococcal Neonatal Osteomyelitis

To the Editor.—Memon et al in a recent issue of the JOURNAL (133:921-923, 1979) emphasized the increasing importance of group B streptococcal neonatal osteomyelitis. Reviewing 23 published cases, they found infection most frequently in the humerus or femur, and occasionally in the talus or tibia. Earlier reports[1] had suggested almost exclusive involvement of the humerus. We recently encountered a case with infection in a previously undescribed location that caused us diagnostic problems.

Report of a Case.—This previously healthy boy was noticed at 13 days of age to be favoring his right leg, holding it flexed at the hip. Two days later fever and irritability developed.

On admission to the hospital, he was febrile (37.7 °C) and irritable, and held his right hip flexed and slightly rotated externally. Movement of the hip obviously caused pain, although the passive range of motion was not limited. An area of cellulitis had recently developed on the dorsum of the right hand. The remainder of the examination results were normal. Roentgenograms of the chest, pelvis, and hips were normal. Lumbar puncture and analysis results revealed normal CSF. The sedimentation rate was 83 mm/hr. Blood cultures subsequently grew group B streptococcus type III.

The right hip joint and femoral metaphysis were aspirated, but no pus was found and cultures of the scant tissue fluids grew no pathogens. The following day, a bone scan with technetium Tc 99m and methylene diphosphate showed increased uptake in the right sacroiliac area, but not in the femur or hand. No physical findings were discernible in the sacroiliac area. Ten days after admission, repeated roentgenograms showed periosteal new bone formation in the medial portion of the right iliac (greater sciatic) notch.

After surgery, antibiotic therapy was initiated with cloxacillin sodium monohydrate, ampicillin sodium, and gentamicin sulfate, and was later revised to penicillin G potassium (200,000 units/kg/day) and gentamicin sulfate (7.5 mg/kg/day for seven days). The area of cellulitis disappeared after two days of therapy and the right hip was freely mobile after three days. He was discharged after 21 days of intravenous treatment and remained healthy during the subsequent three months.

Comment.—Pelvic osteomyelitis is uncommon, causing only 2.5% of the cases in neonates[2] and older children.[3] Diagnosis can be difficult, as the clinical features simulate pyarthrosis of the hip, but passive movement of the hip remains free and point tenderness may be present over the affected area of the pelvis, if accessible. Internal subperiosteal collections of pus may be evident by rectal examination, ultrasound study, or cause displacement of the bladder on an intravenous pyelogram. Radioactive nuclide scanning has been very helpful in revealing sacroiliac infection.[4]

In this patient, pelvic osteomyelitis occurred as a complication of late-onset group B streptococcal bacteremia, a localization to our knowledge not previously described. No predisposing factor was apparent: the baby was not delivered from a breech presentation nor was there any sign of local bruising. As experience increases, group B streptococci will likely prove capable of infecting any bone.

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Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection.*
Cloxacillin sodium monohydrate—*Tegopen.*
Gentamicin sulfate—*Garamycin.*

1. Edwards MS, Baker CJ, Wagner ML, et al: An etiologic shift in infantile osteomyelitis: the emergence of the group B streptococcus. *J Pediatr* 93:578-582, 1978.

2. Fox L, Sprunt K: Neonatal osteomyelitis. *Pediatrics* 62:535-542, 1978.

3. Edwards MS, Baker CJ, Granberry WM, et al: Pelvic osteomyelitis in children. *Pediatrics* 61:62-67, 1978.

4. Trauner DA, Connor JD: Radioactive scanning in the diagnosis of acute sacroiliac osteomyelitis. *J Pediatr* 87:751-753, 1975.

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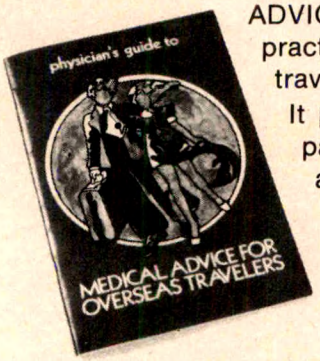

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Books

Fifteen Thousand Hours: Secondary Schools and Their Effects on Children, by Michael Rutter, Barbara Maughan, Peter Mortimore, and Janet Ouston, 285 pp, Cambridge, Mass, Harvard University Press, 1979.

We have come a long way from the heady days of the Great Society, when most people seemed to believe that education would solve all of our problems, both intellectual and social. The Coleman Report in 1966 cast the first doubts, and Jencks (*Inequality*) and Averch (*How Effective is Schooling?*) in 1972 seemed to make it official: nothing that schools do really makes any difference. Considering that we spend more on schools than most other state and local governmental functions combined, this is indeed a dreary state of affairs.

Fifteen Thousand Hours has the temerity to question our present conventional wisdom. It is a study of what things do make a difference in pupil outputs in 12 London inner-city secondary schools. In many ways, it is a substantial improvement, methodologically, over previous studies. First, it studies not just one output (which has usually been the score on some standardized test), but looks at measures of attendance, behavior, delinquency, and achievement. This is not a simple cross-sectional study, but one that examines the students over the four to six years they spend in secondary school. The researchers gathered data not only on those things for which it is easy to gather data (a practice that limits the usefulness of much social science research), but actually went into the classroom and observed what was happening. The result of all this is a book that is rich in detail and often convincing in argument. Some details here will give the flavor of their conclusions.

The schools described, and the neighborhoods they serve, sound as if they could be in almost any American inner city. The houses are old, overcrowded, and rundown. The students have high rates of delinquency and low school achievement. Parents are mostly of the lower class, and there is much unemployment. The schools are in old buildings on crowded sites. Although there is more organizational variety among the schools than one would find in the United States (single-sex schools and church-related schools, for example), the programs of instruction in all are administered by the Inner London Education Authority and are quite similar. Nevertheless, there are large differences among the 12 schools in average achievement, attendance, behavior, and delinquency, and these differences remain large even when differences in the characteristics of the children entering the schools are taken into account. These outcome measures were of children at about age 16 years, the age at which compulsory schooling ends and most leave the schools, and the controlled characteristics were measured when these children entered the secondary schools at about age 11 years. The controlled characteristics were "verbal reasoning," as a control on innate ability, and parental occupation as a control on family background.

The researchers then looked at a large number of school variables, and correlated these with the four outcome measures. The first finding was that physical and administrative features of the schools had no apparent influence on outcomes. Sex composition and religious orientation were unimportant. Size of student body and square feet of building space per student showed no effect. Pupil-teacher ratios similarly had no observable influence. When the researchers looked at variables reflecting the schooling process, however, they began to find significant associations. Some variables representing the school's academic emphasis showed significant correlations with some of the outcome measures. Most of the variables that measured teacher actions during lessons (such as percent of teaching time spent on the topic, and number of disciplinary interventions) were significantly correlated with behavior, but not with the other outcome measures. The association between punishment and outcomes was not usually significant, but that between praise and outcome often was.

This brief summary can only hint at the wealth of data that are summarized and discussed in the book. It warms the cockles of an educator's heart to think that what he is doing is having a worthwhile effect on pupils after all. Unfortunately, a few strong words of caution are necessary. First, the study is of just 12 schools. When the school is the unit of analysis, there is a limit to the things that can be held constant while others are explored. Also, of course, one wonders how the findings can be generalized to dissimilar schools. Second, the controls in inputs are not as stringent as one might desire. Scores on verbal reasoning were "held constant" by discarding the top and bottom 25% of the pupils on this measure, and looking at the middle 50%. Similarly, parental occupation, which is supposed to control for family influences, was collapsed into only three occupational categories.

There are a number of other criticisms one might make of the statistical procedures, including the fact that causation cannot validly be inferred from correlation. In the authors' defense, it must be said that they seem to be fully aware of these shortcomings. The problems arise from the nature of the data available, even though this is a thorough, carefully done study in which a massive amount of data was gathered. The study clearly points up the dilemmas facing those who would perform research in the social sciences. The varieties of human behavior are so numerous, and their interactions so complex, that acquiring reliable knowledge in all but the smallest corners is incredibly complicated. This study is an example of a type of research that should be done more often. The results should be read with interest by educators everywhere. They should not be considered proved, however, until a number of other studies are performed that reinforce the findings.

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Epilepsies of Childhood, by Niall V. O'Donohoe 318 pp, Washington, DC, Butterworth Inc, 1979.

This is an excellent, small volume that covers in a comprehensive fashion almost all aspects of clinical problems in epilepsy. It is also timely in its publication, in that it has been about eight years since Livingston's book was first published, which recently has been the standard pediatrically oriented monograph on epilepsy. Dr O'Donohoe provides comprehensive discussion of the clinical problems, as well as updates our information. In addition to the expected coverage in chapters relating to such problems as "neonatal seizures," and "Major Generalized Epilepsy (Grand Mal)," etc, there is also the very convenient and

concise presentation of a number of special problems in epilepsy, such as "Post-Traumatic Epilepsy," "Epilepsy in the Adolescent," "Learning Problems in Children with Epilepsy," "Epilepsy in Sleep," etc. These issues are presented in brief chapters and provide a balanced account of the particular problem, which is useful for quick reference, rather than burying the information in larger chapters. However, the brief chapter on "Epilepsy in Brain Tumors," although correctly pointing out the rarity of supratentorial tumors in childhood that appear as a seizure problem, does not deal with the occasional but important instances of long-standing epilepsy in childhood (up to 90% of the lifetime of a 10- to 15-year-old child) where tumor is eventually revealed as the cause. This possibility reinforces the importance of alert reassessment of chronic epilepsy patients on follow-up examination.

The advantage of a single author who speaks from a significant personal experience is obvious in monographs of this kind. The bias of the author, however, occasionally shows itself. I was struck by a number of references that indicate he may be too hard on phenytoin, a drug that continues to be very useful despite an increasing list of problems relating to chronic toxicity. A more positive prejudice is the balanced place that the EEG is given in this account. Some would say it is underemphasized; I think, however, that in a presentation to students and pediatricians it is entirely appropriate. In summary then, I am pleased to have a copy of this book and plan to use it.

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Liver and Biliary Tract Disease in Children, by Daniel Alagille and Micheal Odievre, 364 pp, New York, John Wiley & Sons Inc, 1979.

This concise monograph fills a large gap on the pediatrician's bookshelf. Its pages document the rich clinical experience of Drs Daniel Alagille and Michelle Odievre in conjunction with several collaborators from the pediatric liver research unit at the Hôpital de Bicêtre, Université Paris Sud. The chapters are not individually authored, and the overall quality is assured by multidisciplinary teamwork. The translation from the French by Micheline Ste-Marie of the Pediatric Gastroenterology Unit at Laval University, Quebec, reads remarkably well. However, an occasional awkward word or phase provides more syllables than most Americans would care to pronounce, for example, "syndromatic" vs "nonsyndromatic" versions of a cholestatic disorder initially described by Alagille in 1949. In "nonsyndromatic" patients with isolated cholestasis secondary to paucity of interlobular bile ducts, hepatic disease is severe and may follow prenatal or postnatal infection. Patients with the autosomal dominant, "syndromatic" form have characteristic facies, cardiovascular malformation, vertebral arch defects, and milder chronic liver disease.

The book begins with a critique of various clinical, radiologic, and laboratory methods used in defining pediatric hepatobiliary disease. Indications, limitations, and relative risks are dogmatically and succinctly presented. This forthright style reflects an extensive personal experience with the gamut of invasive and noninvasive procedures. Superb organization and several summary tables provide an amazing amount of information in usable form. Illustrations, particularly the photomicrographs, are of exceptional quality.

Each chapter is amply referenced from both the American and European literature. Since the original French edition antedated the English translation by about one year, more recent literature may be missing. Using the index can be frustrating and disappointing. This may reflect an exaggerated expectation on the part of the reader. This book was never intended to be an encyclopedia of pediatric liver disease, although it is tempting to refer to it as such because of the enormous amount of material contained within these brief chapters. In many instances, not only is the state of the art surveyed but prospective research developments noted as well. Numerous exciting questions are raised and it is to be hoped that answers will be found in future editions. For example, the chapter on the liver in systemic disease points out that the articular symptoms of patients with juvenile rheumatoid arthritis often improve during episodes of viral hepatitis. This phenomenon is not observed in lupus erythematosis. The poorly understood immunologic reactivity of these patients remains to be studied.

It is surprising to learn that the authors have no personal experience with Reye's syndrome. Only eight cases have been reported in France to date. The six-page chapter, therefore, represents a short literature review of the subject. This contrasts sharply with the in-depth analysis of the various forms of hepatitis. Similarly, the chapter on inborn errors of metabolism adequately reviews a 16-year experience at Hôpital d' Enfants de Bicêtre yielding 52 patients with hereditary fructose intolerance and nine patients each with galactosemia and tyrosinemia. The glycogenoses, cystic fibrosis, and Wilson's and Wolman's diseases are also well covered. However, the classification of storage disease fails to mention generalized gangliosidosis (Landing's disease). Severe hepatomegaly occurs in this disorder, and the initial diagnostic suspicion may be aroused during the assessment of the liver biopsy specimen in the appropriate clinical setting. The authors avoid discussing lysosomes and do not show any representative electron micrographs. This may be appropriate for a book intended primarily for clinical use.

Liver pathology associated with total parenteral nutrition is not covered. The inspissated bile syndrome is briefly mentioned and said to have a hemolytic basis. Also, references to bile acid metabolism are essentially absent. It may be particularly interesting to study bile acids in Alagille's disease since Byler's disease, another familial cholestatic syndrome, is associated with high lithocholate levels. In Byler's disease, metabolic cirrhosis may be complicated by hepatoma, and in Alagille's disease, portal fibrosis may be moderate to absent. The interplay between cholestasis and cirrhosis in a variety of metabolic diseases required further clinical and experimental emphasis on the formation and circulation of bile.

As one would expect, there are some discrepancies between the European and the American classifications of hepatobiliary disease. Some pediatric pathologists would classify the hamartomatous fibrocystic lesions of congenital hepatic fibrosis as part of the spectrum of infantile polycystic kidney disease since an occasional pedigree shows autosomal recessive inheritance of both phenotypes. Dr. Benjamin Landing's unitary hypothesis refers to neonatal hepatitis, biliary

atresia, and choledocal cyst as various facets of the same disease process, which he calls infantile obstructive cholangiopathy. As the chapter title indicate, the French workers consider these to be distinct entities. Their major argument is based on the absence of any serologic evidence of antecedent viral infection in patients with extrahepatic biliary atresia and the exceptional occurrence of histologically confirmed intrahepatic and extrahepatic biliary atresia in the same patient.

In his preface, Prof Alagille states this book was conceived 15 years ago. His legacy is worthy of such a long gestation. This marvelous monograph permits the non-French-speaking physician to telescope the bedside teaching rounds and experience derived from one of the world's major centers for pediatric liver disease. Physicians challenged by pediatric hepatic disease will greatly appreciate this book.

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Books in Brief

Examination of the Child With Minor Neurological Dysfunction, by Bert C. L. Touwen (141 pp, Philadelphia, JB Lippincott Co, 1979). This how-to-examine text deals with an admittedly difficult area of medical, neurological, and psychological endeavor. The author introduces the subject with a thoughtful review of the enduring debate over minimal brain dysfunction: its definitions, boundaries, and meanings. A discussion of important caveats on the interpretations of neurological signs gives a sense of the turbulence in this complicated field. The neurological examination is described and photographically illustrated in its various components. A standard method of testing is given for each part of the examination, with notations on the recording of performance. A number score system is introduced that codes the performance independently for each component tested. The results are intended to demonstrate a profile of performance and are in no way additive when put on the score sheets. The complexity of the examination and the scoring system suggests that this text would be most useful to those who work in evaluation clinics for such types of disorders, where in-depth study, review, and research might help to add new understanding to this field.

Handbook for Differential Diagnosis of Infectious Diseases, by Johnas A. Shulman, David Schlossberg (280 pp, $13.50, New York, Appleton-Century-Crofts, 1980). This is a purely clinical textbook, designed to be of use to the physician faced with a diagnostic problem. When you must decide what entities to consider in a pneumonia, an "infectious looking" rash, or the interpretation of test findings of the CSF, you will find this well-organized book of value. The section headings deal with "presenting symptom" or "signs," such as diarrhea, jaundice, or splenomegaly. Disease entities subsumed under these categories are discussed briefly, with the stress on the differential aspects of each. The second half of the book consists of charts of the same groups of entities, deals here with the more commonly encountered, treatable conditions, and outlines them in terms of cause, signs, diagnostic studies, and therapy. Of value also are a number of subjects in the appendix. Hematologic changes in various infections, the handling and culture of specimens, and special serologic and skin testing methods are but a few of these useful tools and suggestions. The emphasis is almost exclusively on adult disease states. It should be of great value to house officers, internists, generalists, and those who do a volume of inpatient work. Its small size, soft cover, and affordable price enhance the value of this useful book.

Developmental Disabilities: Etiologies, Manifestations, Diagnoses and Treatments, by Robert J. Thompson, Jr, Aglaia N. O'Quinn (308 pp, $13.95, New York, Oxford University Press, 1979). This book is well researched and well written. The authors, a psychologist and a pediatrician, have done a good review of the literature on a number of important disorders that are included under the term "developmental disorders." For each subject, a historical perspective is given and a resume presented of the clinical manifestations. Infantile autism, for example, is well described, even to the extent of discussing the conflicting views held by various authorities on its cause. References for each chapter are up-to-date and well selected. The causes, manifestations, and diagnostic aspects seem well covered for the most part. Treatment, particularly the concept and implementation of a multidisciplinary approach, seems somewhat scantily handled. By comparison with many thoroughly handled disorders, such as cerebral palsy, subnormality, and seizure disorders, the sensory disorders of speech and hearing seem less thoroughly described. This volume is surely of value to physicians, nurses, and paramedical personnel, but is perhaps overly complex for teachers and those without prior medical training.

The Epileptic in Home, School, and Society: Coping With the Invisible Handicap, by Stephen W. Freeman (285 pp, $14.75, Springfield, Ill, Charles C Thomas Publisher, 1979). This book serves a most important need. It puts together a vast array of information that deals with the world of the epileptic: the medical dimensions of his problem, its causes, treatments, and outlook. The book covers what he can expect to encounter in a world of prejudice, misinformation, and fear as he goes to school, seeks work, and builds a career, and to whom he can turn for help, for answers to hundreds of questions of his rights and his life's prohibitions, for military service, for a driver's license, and for genetic counseling about a family of his own. The author writes well and has assembled an impressive body of facts on these issues. There are good, sensible bits of advice to parents about avoiding overly permissive and solicitous attitudes in child rearing, including advice about giving daily medications to the balky child. The physician might want to loan this book to parents or patients. Nonmedical professionals—teachers, counselors, social workers, therapists of all kinds—should consider having a copy.

Practical Pediatric Dermatology, by William L. Weston ($19.95, Boston, Little Brown & Co, 1979). With the stated purpose of presenting dermatology in an abbreviated form, stressing essentials, this book succeeds admirably. Each disease state is presented in a clear, systematic, orderly style. Two additional elements are

incorporated in the description of each entity: a section titled "Patient Education"; and a suggestion on follow-up visits. Both are seldom mentioned in other dermatology texts. A well-written, comprehensive chapter on dermatopharmacology provides the reader with a sensible, understandable background of general principles of therapy. By reading this section carefully, the clinician should derive much valuable information for his therapeutic methods, so that he is able to apply good-sense management even if he is uncertain on precise cause. Pictures are black-and-white and some lack clarity of detail. However, the expediency of avoiding color photographs keeps the book at a very affordable price. I suspect this will be a popular and useful desk-top reference for most people who find themselves repeatedly puzzled by the rashes of childhood.

A System of Newborn Physical Examination, by John W. Scanlon, Thomas Nelson, Lawrence J. Crylack, Yolande F. Smith (96 pp, $8.95, Baltimore, University Park Press, 1979). How does one go about examining the newborn? This book describes in some detail the elements of the newly born infant: his physical characteristics, the assessment of gestational growth, and neurological and behavioral performance. It pulls together many aspects of neonatal assessment that at present may be widely scattered, such as Dubowitz's scale, Apgar scoring, neurological assessment, the Silverman scoring of respiratory functioning, and normal blood pressure levels. The technique of examination is taken up on a regional basis, for example, as musculoskeletal, abdomen, skin, hair and nails, and the like. At the end, a series of seven cases is presented that illustrates how the findings on examination are synthesized into a meaningful working diagnostic pattern. Appropriate laboratory and other studies are then suggested. This chapter seems very worthwhile, albeit brief. This book seems most appropriate for those who have had limited prior exposure to neonatal infants. It should be used in conjunction with other, more detailed, textbooks that deal with specific entities.

A Vision Fulfilled: The Story of the Childrens Hospital of Winnipeg 1909-1973, by Harry Medovy (156 pp, $12.50, Winnipeg, Manitoba, Canada, Peguis Publishers Ltd, 1979). This is a heartwarming account of a community and its children's hospital, aged 70 this year. The author writes from his 50 years of personal contact, 16 of which were as chief-of-staff. Its founder, Mrs J. R. H. Bond, a nurse, had settled in Winnipeg in 1903. Within several years she had stirred an intense community interest in starting a children's hospital. In 1909, the hospital opened in a converted private house; by 1911 it had moved to a newly erected building. Anecdotes abound in this very personable history. I particularly liked one about the open-sided elevator in the center of the building. It moved so slowly that those walking on the stairway around it could hold their consultations with its trapped occupants. Some of the hospital's renowned medical staff members are remembered in a series of profiles. Its nursing school is prominently reviewed; a complete listing of nurse graduates is given from its first in 1913. Dr Medovy is particularly attentive to giving credit and paying respect to nonmedical supporters of the hospital over its years, obviously a clue to the continued success of the voluntary hospital. The book is nicely illustrated with old photographs. It has a complete index from which the author has modestly excluded himself.

The Clinical Practice of Adolescent Medicine, by Jerome T. Y. Shen (727 pp, $36.50, New York, Appleton-Century-Crofts, 1980). This is a large and comprehensive text that deals exclusively with the adolescent. It is multiauthored by a large number of experts in the field of adolescent medicine and surgery. Largely clinical in direction, there is much difference in styles of presentations; sometimes being very clinical, sometimes quite theoretical. A number of areas receive timely emphasis, such as coronary artery disease, smoking and drug use, sports medicine, and physical fitness. With some clear exceptions, the general emphasis of this text is on disease states and factual material, which seems to be up-to-date and well referenced. There are many physicians who struggle in the care of adolescents and who voice concern about their own ability to cope with adolescent behavior: those devious ways, self-destructive acts, and confused statements. There is little discussion here on how such physicians may understand better and deal more effectively with such behaviors. Coverage of topics is in some areas a bit erratic. Osgood-Schlatter disease is discussed twice. The sex maturity rating scales described in one chapter do not interrelate with those used in the discussion of delayed menarche in the gynecology chapter. Rape is only briefly mentioned, with no advice provided on the sensitive issues of the examination of rape victims. Obesity, described in the text under morbidity as "the most common diagnosis among organic diseases" is handled in a scant two pages. With limitations, this text is a good addition to reference source material on the adolescent.

Health and the Family, edited by Clive Wood (239 pp, $27, New York, Grune & Stratton Inc, 1979). This book contains the proceedings of a symposium held in Cincinnati in May 1978, which was sponsored jointly by the Royal Society of Medicine and the Royal Society of Medicine Foundation. Most of the 27 participants were physicians, 19 of them being from the United States. The subject matter can be grouped into three broad categories: the family itself, the physicians who look after families (or parts of families), and the education of physicians for family care. Underlying and intertwining with most of the discussion is a comparison of two diverse societies, the United States and the United Kingdom. Each of the talks has been carefully edited and referenced. The questions and answers and discussion on each topic are included at the end of each section. All of us who deal with families will find much of great interest in this little volume, irrespective of our viewpoints. One surprising and significant inclusion in the series of topics is the family and the media, which discusses not only the effects of television on family life, but the uses of the media in furthering public education in medicine. This was a timely and interesting conference, one well worth reading. Its presented material seems to have been carefully edited by a tireless staff person who has modestly refrained from any mention of himself apart from the title of "editor."

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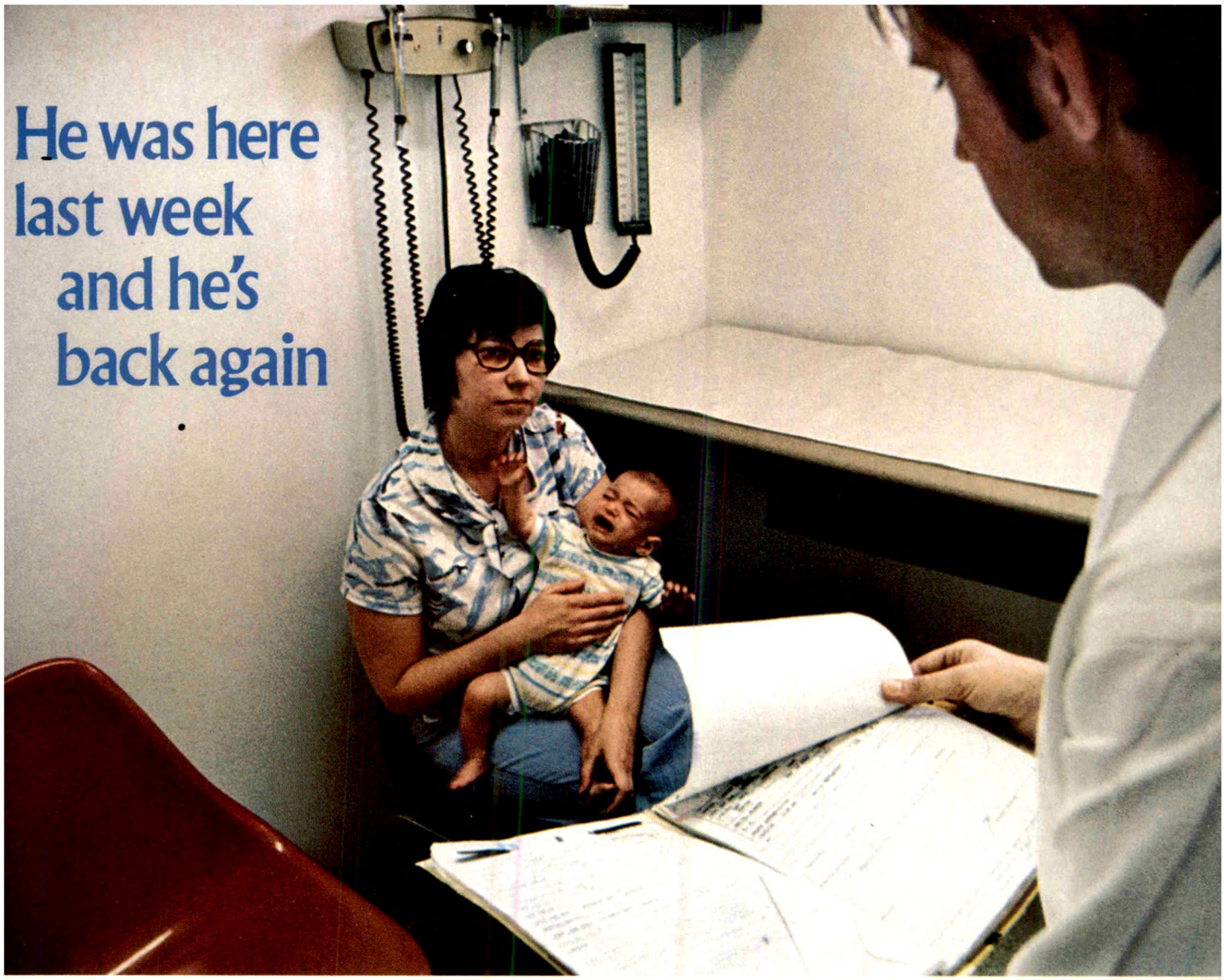

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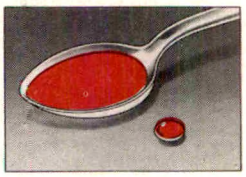

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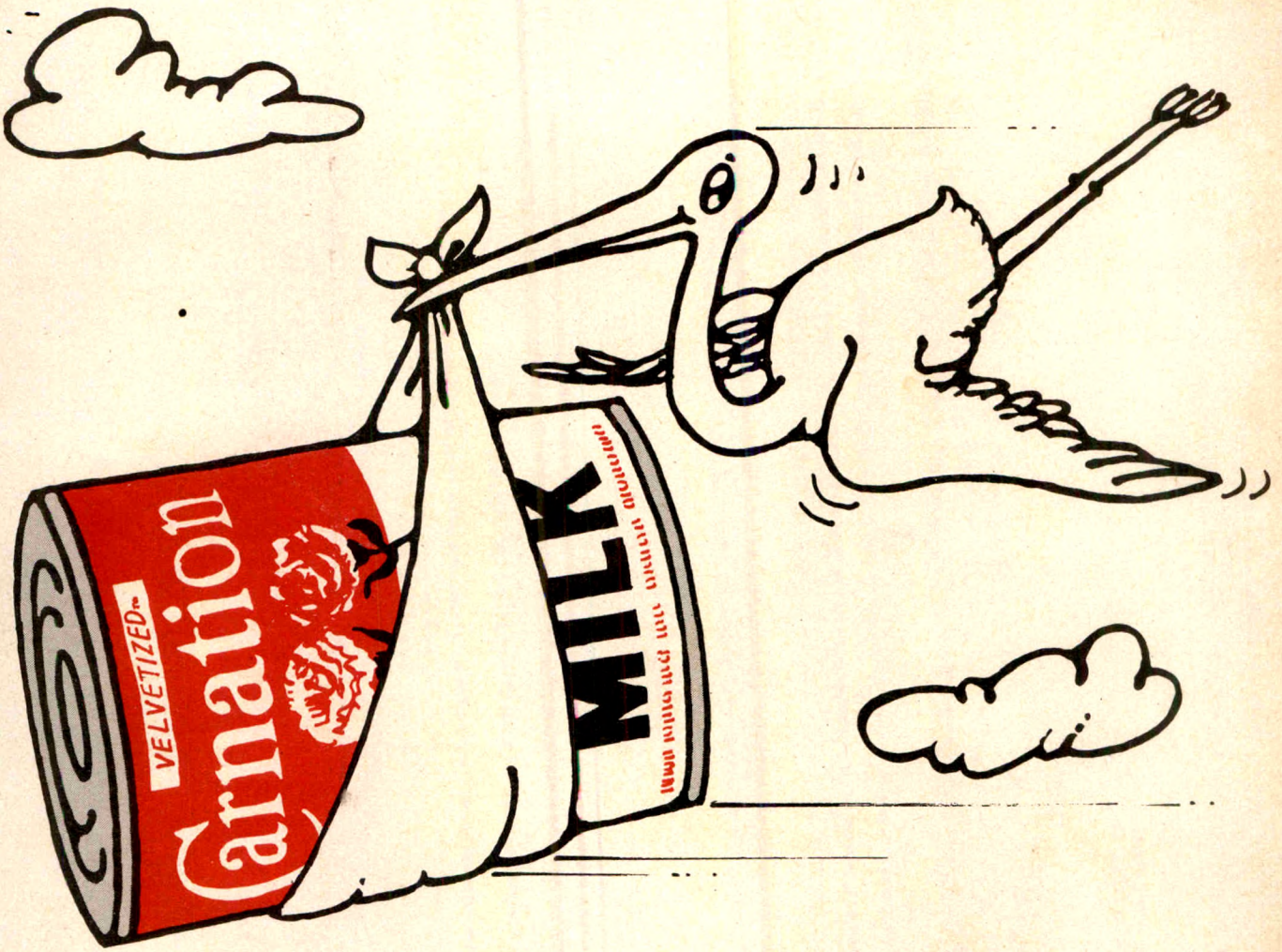

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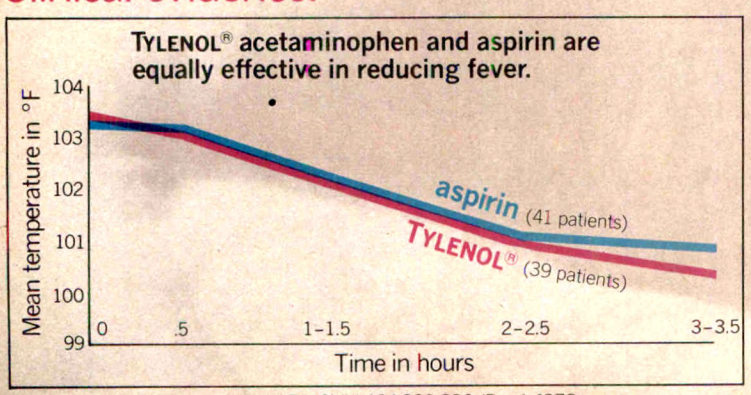

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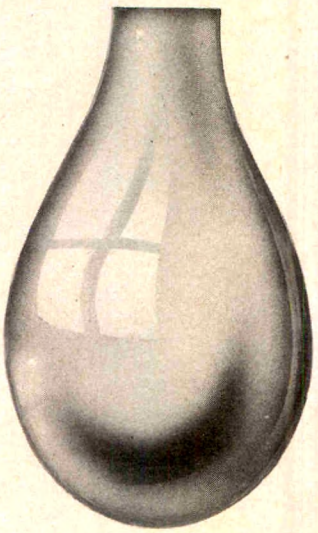

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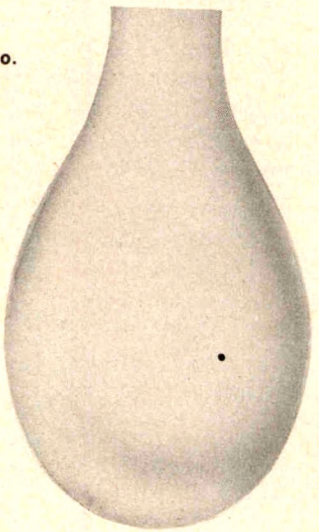

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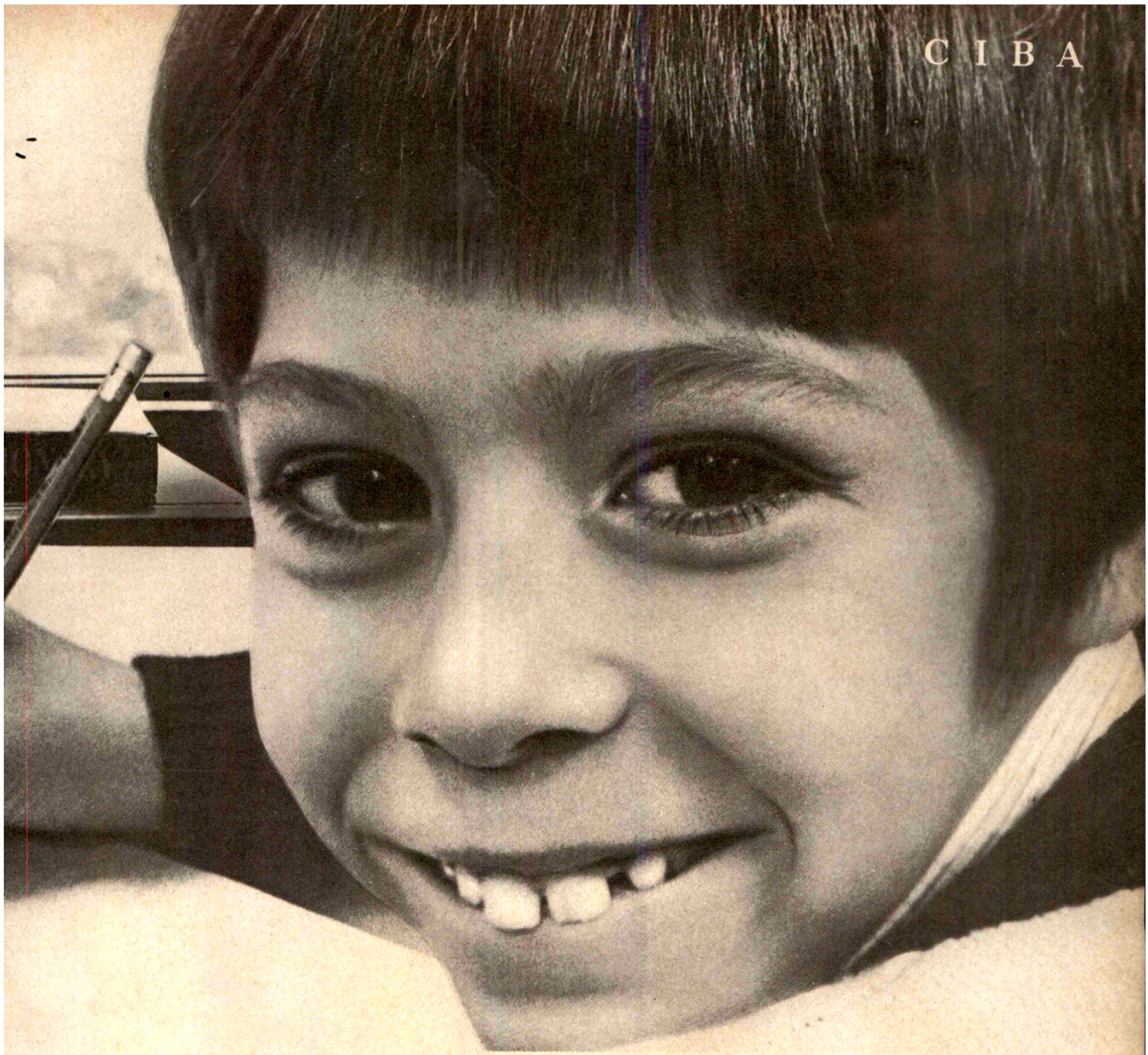
A 20-year record of proven efficacy

Over the years, Ritalin has become an established choice for pharmacotherapy of ADD. In a report by the



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National Council on Child Health,[1] Ritalin was described as among the most effective and best-documented agents for stimulant therapy in hyperkinetic children.

Reduces hyperactivity, impulsive behavior

Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

Generally well tolerated

Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

*Attention Deficit Disorders: new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

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TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Tablets, 20 mg (peach, scored); bottles of 100 and 1000.

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Tablets, 5 mg (pale yellow); bottles of 100, 500 and 1000.

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References

1. Kugel RB, Scherz RG, Seidel HM, et al. Council on Child Health. Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4):560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al. Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30**:354-359.
3. MacKay MC, Beck L, Taylor R. Methylphenidate for adolescents with minimal brain dysfunction. *NY State J Med* 1973 (Feb.); **73**:550-554.

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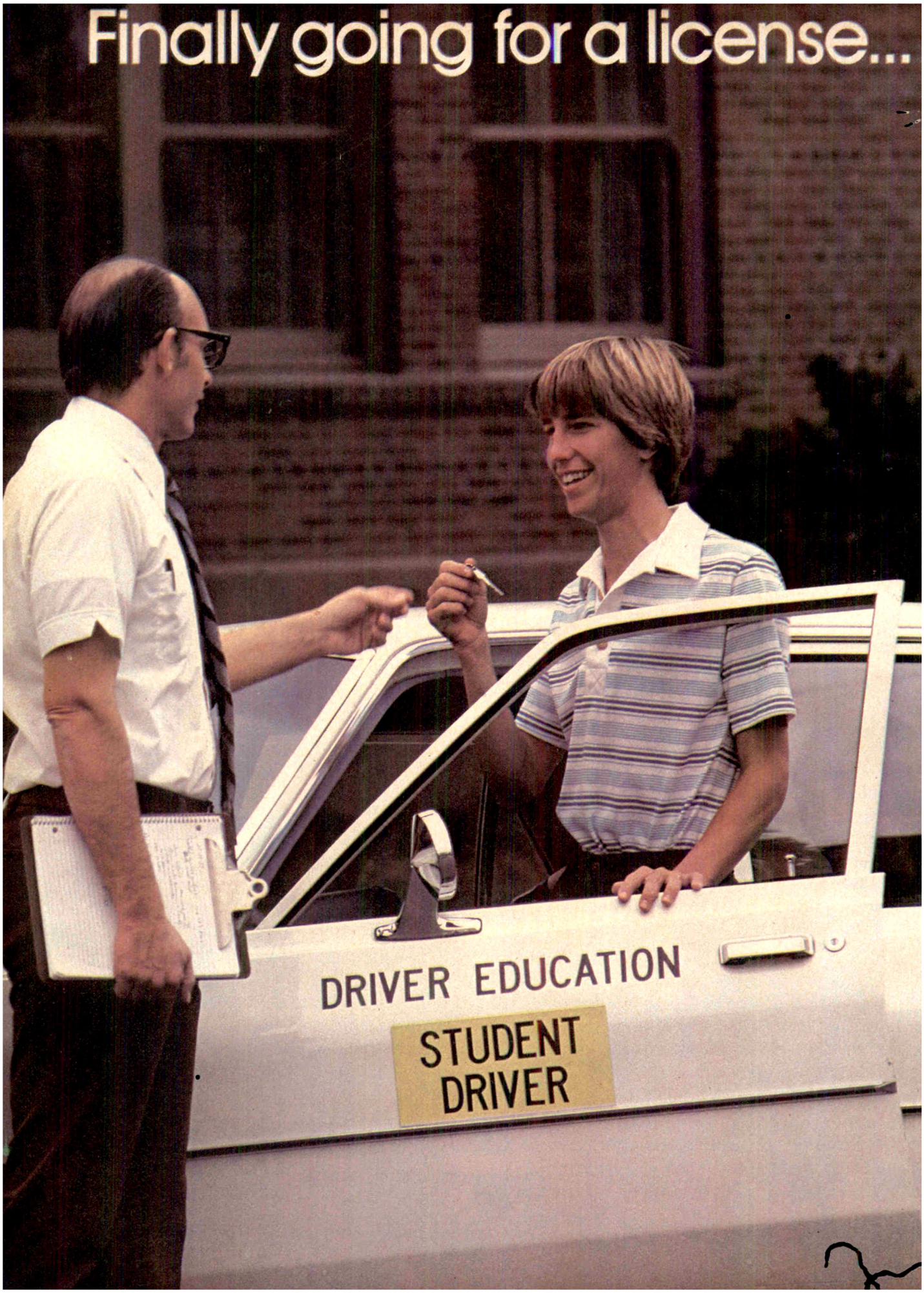
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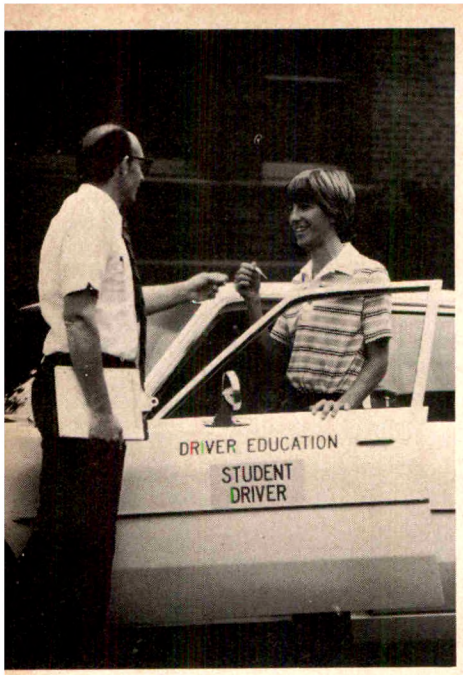

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PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported but do not appear dose related. (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increased dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

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Sleep Hypoxemia in Patients With Cystic Fibrosis

Two important issues are involved in the demonstration of sleep hypoxemia in patients with cystic fibrosis. First, the degrees of arterial oxygen desaturation presently shown by Francis et al (see p 734) may be great enough to accelerate the progress of cor pulmonale. Second, disturbance of the normal sleep pattern is a problem recognized by patients with advanced pulmonary disease. It certainly worsens their quality of life and may well hasten the course of the disease itself.

Relationships between sleep state and breathing are now studied with great interest by researchers in respiratory physiology, neurophysiology, and anesthesiology. New techniques allow meaningful descriptions of sleep state, activity of respiratory muscles, mechanics of breathing, and changes in arterial blood gas levels. However, the pertinent questions arose from clinical observations. Adults with severe chronic obstructive pulmonary disease have long been known to suffer reversal of the normal sleep pattern; they have increasing wakefulness at night and somnolence during the day as their hypoxemia worsens.[1] Some respiratory physiologists involved in the care of such patients have resided at high altitudes and have experienced sleep disturbance themselves. Subsequent studies of normal subjects sleeping at high altitudes have shown profound oxygen desaturation associated with periodic breathing, partly uncovering the cause of mountain sickness.[2] Pediatricians have observed that children with the syndrome of upper airway obstruction and cor pulmonale often fail to provide convincing evidence of obstruction while awake. Now we know that apparently normal middle-aged men may suffer bouts of arterial oxygen desaturation with upper airway obstruction while asleep[3] and that muscular control of upper airway patency is defective in certain sleep states.[4] Obesity has long been implicated as a cause of hypoventilation during sleep and we now recognize that obese persons may breathe at very low lung volumes in the supine position, predisposing to airway closure and increasing the work of breathing.

Patients with cystic fibrosis are rarely obese and do not show propensities for either upper airway obstruction or periodic breathing while asleep. Why are they predisposed to sleep hypoxemia? In some stages of rapid eye movement (REM) sleep, intercostal muscle tone is greatly diminished and central respiratory drive irregular.[5] Francis et al found slight hemoglobin desaturation in their group of young adult controls during REM sleep, but more severe desaturation in their patients. In a recent study of young adults with cystic fibrosis, Stokes et al (see p 741) detected the uncoupling of abdominothoracic motion that would be expected from a large decrease in intercostal muscle tone during REM sleep. These events were associated with significant arterial oxygen desaturation. Therefore, it seems that a normal change in control of respiration, rather than one unique to the patients, decreases lung capacity during sleep. In young, normal adults, such a decrease in lung capacity has little or no effect on gas exchange. Since most teenagers and young adults with cystic fibrosis are already hypoxemic and have airway closure at abnormally high lung volumes, they suffer deterioration of gas exchange when breathing at low lung volumes.

Progressive increases in pulmonary arterial pressure may occur in adults who have repeated bouts of arterial desaturation from the sleep apnea syndrome. Therefore, it may seem a foregone conclusion that supplemental oxygen should be used to prevent desaturation in those patients who show it. But the present study and the report by Stokes et al found the most severe degrees of desaturation in the patients with the most advanced lung disease. These patients are likely to have carbon dioxide retention and some will respond to supplemental oxygen by marked decreases in ventilation. Since oxygen therapy is particularly likely to become intermittent in the sleeping, unattended patient, it can cause previously unexperienced depths of oxygen desaturation whether any changes due to sleep itself occur or not. Even if the inspired concentration of oxygen is steady, a decrease in ventilatory drive may cause retention of secretions. It follows that patients with the most advanced lung disease present the greatest need both for supplemental oxygen and for a controlled setting to evaluate its effect. Sykes et al have contracted this first principle of controlled oxygen therapy into a formula[1]: "If intermittent oxygen therapy is safe, it is unnecessary. If oxygen is needed, it is dangerous."

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New York, NY 10032

References

1. Sykes MK, McNichol MW, Campbell EJM: *Respiratory Failure*, ed 2. London, Blackwell Scientific Publications, 1976.
2. Sutton J, Houston C, Mansell A, et al: Effect of acetazolamide on hypoxemia during sleep at high altitude. *N Engl J Med* 301:1329-1331, 1979.
3. Block AJ, Boysen PG, Wynne JW, et al: Oxygen desaturation in normal subjects. *N Engl J Med* 300:513-517, 1979.
4. Remmers JE, deGroot WJ, Sauerland EK, et al: Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 44:931-938, 1978.
5. Phillipson EA: Respiratory adaptation in sleep. *Ann Rev Physiol* 40:133-156, 1978.

Hemoglobin Desaturation

Its Occurrence During Sleep in Patients With Cystic Fibrosis

Paul W. J. Francis, MB, BS, FRACP; Nestor L. Muller, MD; Dennis Gurwitz, MB, BCh, FRCP(C); David W. A. Milligan, MB, BS, MRCP; Henry Levison, MD; A. Charles Bryan, MB, BS, PhD, FRCP(C)

• Sleep studies were performed in 20 clinically stable cystic fibrosis (CF) patients (mean age, 18.2 years) to determine the magnitude of fall in hemoglobin saturation (Sao_2) during sleep and to relate these changes to pulmonary function and echocardiographic findings. Five healthy young adults served as controls. In both groups, the maximum fall in Sao_2 was seen during rapid eye movement (REM) sleep. The mean maximum fall in the control group during REM sleep was 2.0% (range, 1% to 3%), compared with 7.4% (range, 1% to 23%) in the CF group. Of the 11 patients in whom right ventricular systolic time intervals were obtained, eight of the nine patients with falls in Sao_2 greater than 3% during REM sleep had echocardiographic evidence of pulmonary hypertension. Repeated episodes of desaturation during sleep may contribute to the development and progression of cor pulmonale in CF patients.

(*Am J Dis Child* 134:734-740, 1980)

Cor pulmonale is a common complication of cystic fibrosis (CF). Autopsy studies have reported an incidence of 70% to 80%.[1,2] Although the prognostic significance of mild pulmonary hypertension is not fully known, once overt right ventricular failure has developed the prognosis is extremely grave,[3,4] with a median survival in one series of only months.[5]

Hypoxia is thought to be the major etiological factor in the development of cor pulmonale in CF.[6,7] Studies in adults with chronic obstructive lung disease (COLD) have demonstrated repeated episodes of falls in hemoglobin saturation (Sao_2) during sleep[8-10] associated with transient pulmonary hypertension.[11,12] It has been suggested that in some patients these episodes may eventually lead to sustained pulmonary hypertension and cor pulmonale.[11-14]

Recently, it was shown that CF patients frequently have echocardiographic evidence of cor pulmonale that would not have been expected on the basis of their pulmonary function data or waking Pao_2.[15,16] Therefore, we investigated the incidence of hemoglobin desaturation during sleep in CF as a possible etiological factor in the development of cor pulmonale. As there are conflicting data on the magnitude of hemoglobin desaturation during sleep in apparently normal older adults,[9,12,17-20] a group of healthy young adults was also studied to serve as a control.

From the Division of Respiratory Physiology, Research Institute, Hospital for Sick Children, Toronto.

Reprint requests to Pulmonary Function Laboratory, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (Dr Levison).

MATERIAL AND METHODS

The patient group consisted of 20 CF patients (nine female and 11 male) with a mean age of 18.2 years (range, 8.8 to 29.3 years). All were studied when their pulmonary status was stable as assessed by clinical, radiological, and pulmonary function criteria. The patients were selected solely by their willingness to participate in the study.

The control group consisted of five nonobese young adults (three women and two men) with a mean age of 26.7 years (range, 22.4 to 30.4 years). None had a history of lung disease, cigarette smoking, snoring, or sleep disturbance.

The sleep studies were commenced at the usual time of retiring (usually around midnight), and were continued until around 6 AM. The EEG was recorded as a bipolar single channel from surface electrodes placed in the left frontal and parietal regions. The electro-oculogram was recorded from a pair of electrodes placed at the outer canthus of each eye. Hemoglobin

saturation was monitored with an ear oximeter. Rib cage and abdominal movement were monitored by linearized magnetometers placed in the midline at the level of the nipple and at 1 cm above the umbilicus, respectively. In all subjects, the signals were recorded on an eight-channel recorder. The subjects were observed throughout the sleep study to note the presence of snoring, as well as positional or behavioral changes.

To examine the reproducibility of the sleep study findings, two CF patients had repeated studies performed several weeks after the initial study. For the second study, each subject had pulmonary function results similar to those measured at the time of the initial study.

Sleep state was assessed as wakefulness, rapid eye movement (REM) sleep, or non-REM sleep, according to standard criteria.[21] All Sao_2 values subsequently referred to are taken as the minimum values for each sleep state. Falls in Sao_2 values during sleep were calculated from the minimum waking Sao_2.

Pulmonary function studies were performed in CF and control subjects within 24 hours of the sleep study. Thoracic gas volume (TGV) and airways resistance (RAW) were measured in a constant volume body plethysmograph. In two patients in whom RAW and TGV were not measured, functional residual capacity (FRC) was estimated by the helium dilution technique. Inspiratory capacity and expiratory reserve volume were obtained from a 9-L water-filled spirometer, and values for total lung capacity (TLC), residual volume (RV), and RV/TLC were subsequently calculated. Forced vital capacity (FVC), forced expired volume in 1 s (FEV_1), and forced expiratory flow during the middle 50% of the FVC were measured with a Wedge spirometer. Results for TLC and flow rates were expressed as the percent of normal values for this laboratory.[22] Blood gas analysis was performed in CF patients using arterial (12 patients) or arterialized capillary samples (eight patients).[23] Shwachman-Kulczycki scores were determined in all patients.[24]

M-mode echocardiography was performed with the patients supine and their right shoulders slightly elevated (approximately 30°), using transducers selected for each patient with a commercially available ultrasonoscope connected to a strip chart recorder. Right ventricular anterior wall thickness (RVAW), right ventricular internal dimensions (RVD), and the right ventricular preejection period to ejection time (RV = PEP/ET) ratio were measured and compared with normal values.[25-27] The significance of differences between paired and nonpaired data was assessed with Student's t test.

RESULTS

Control Group

All control subjects had normal pulmonary function. The sleep data for the control group are given in Table 1. The mean minimum Sao_2 during REM sleep (95.4% ± 1.3%) was significantly lower than that for the awake state (97.4% ± 0.9%, $P < .005$). The mean minimum Sao_2 during non-REM sleep (96.8% ± 0.8%) was not significantly different from the minimum waking value. The maximum fall in Sao_2 was 1% in non-REM sleep and 3% in REM sleep. In none of these subjects was the desaturation associated with central apneic episodes (as defined by a cessation of respiratory movement for longer than 10 s), snoring, or paradoxical movement of the rib cage and abdomen.

CF Group

The majority of CF patients had moderate to severe lung disease. This is reflected in the pulmonary function data given in Table 2. It can be seen that there was no significant difference between the sexes with respect to any of the pulmonary functions measured.

The sleep data for the CF group are given in Table 3. There were no significant differences between the sexes with respect to any of the sleep variables documented. Both the largest fall in Sao_2 (23% in patient 9) and the lowest Sao_2 (48% in patient 6) were recorded during REM sleep. The percent of total sleep time monitored during which the patient's Sao_2 was more than 3% below the minimum awake value ranged from 0% to 43% (mean, 7.3% ± 1.8%).

For the CF group as a whole, the mean maximum fall in Sao_2 during REM sleep (7.4% ± 5.7%) was significantly greater than that seen during non-REM sleep (3.5% ± 2.0%, $P < .001$). The mean minimum Sao_2 during non-REM sleep (88.2% ± 7.2%) was significantly lower than that for the waking state (91.7% ± 5.8%, $P < .001$). The mean minimum REM Sao_2 (84.3% ± 11.0%) was significantly lower than both the mean minimum non-REM ($P < .001$) and awake Sao_2 values ($P < .001$). There were significant correlations between the maximum falls in Sao_2 during both REM and non-REM sleep and the severity of the lung disease (Table 4).

On comparing the CF and control groups (Table 5), it can be seen that the mean maximum falls in Sao_2 during both non-REM and REM sleep in the CF group were significantly greater than the corresponding falls in the control group. In addition, the mean minimum Sao_2 for the CF group when awake and during both non-REM and REM sleep were all significantly lower than the corresponding values in the control group.

A consistent feature of the desaturation during REM sleep was the lack of arousal as assessed by behavioral criteria after the maximum falls in Sao_2 (Fig 1). Of the total of 45 REM epochs monitored, in only five was there any suggestion of an arousal response associated with the maximum fall in Sao_2. In these latter five instances, it was not possible to determine if the movements observed represented true arousal responses or merely phasic muscular activity normally seen during REM sleep.

Table 1.—Control Group Sleep Data

Subject/ Sex	Awake, Minimum Sao_2, %	Non-REM* Sleep		REM Sleep	
		Minimum Sao_2, %	Maximum Fall in Sao_2, %	Minimum Sao_2, %	Maximum Fall in Sao_2, %
1/F	97	96	1	96	1
2/F	98	98	0	96	2
3/F	96	96	0	93	3
4/M	98	97	1	96	2
5/M	98	97	1	96	2
Mean/SD	97.4/0.9	96.8/0.8	.6/0.6	95.4/1.3	2.0/0.7

*REM indicates rapid eye movement; Sao_2, hemoglobin saturation.

Table 2.—Cystic Fibrosis Anthropometric and Pulmonary Function Data

	Age, yr	Height, cm	Weight, kg	FVC*	FEV_1	FEF	RAW	RV/TLC,† %	$Paco_2$,‡ mm Hg	$Paco_2$,§ mm Hg	Pao_2,‡ mm Hg	Pao_2,§ mm Hg	Shwachman Score
Women, n = 9													
Mean	16.7	159	41.5	43.8	33.6	21.6	180	60	42	42	59	68	61
SD	3.7	5	3.5	12.0	10.9	12.9	119	10	2	6	8	17	20
Men, n = 11													
Mean	19.4	166	52.6	52.6	37.4	19.7	266	55	41	43	61	61	69
SD	5.2	15	13.7	10.6	13.0	11.1	111	9	2	2	4	3	14
Women vs Men	NS	NS	$P < .05$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Women and Men													
Mean	18.2	163	47.6	48.7	35.7	20.6	223	57	42	42	61	64	66
SD	4.6	12	11.6	11.8	12.0	11.6	120	10	2	4	4	12	17

*FVC indicates forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEF, forced expiratory flow during middle 50% of FVC; and RAW, airways resistance. Number indicates percent of predicted result.
†RV/TLC indicates residual volume/total lung capacity.
‡Arterial.
§Arterialized sample.

Table 3.—Cystic Fibrosis Group Sleep and Echocardiographic Da

		Non-REM*				REM					
Patient/Sex	Minimum Waking Sao_2, %	Duration, min	Minimum Sao_2, %	Maximum Fall of Sao_2, %	Duration of >3% Fall in Sao_2, min	REM Epochs	Duration, min	Minimum Sao_2, %	Maximum Fall Sao_2, %	Duration >3% Fall Sao_2, %	Non-REM and Duration†
1/F	96	149	92	4	0.2	2	41	90	6	2.3	1.3
2/F	92	209	90	2	0	3	51	87	5	0.3	0.1
3/F	96	211	95	1	0	2	54	95	1	0	0
4/F	93	200	90	3	0	2	76	89	4	0.2	0.1
5/F	95	100	93	2	0	2	59	92	3	0	0
6/F	70	115	64	6	28.6	2	45	48	22	40.2	43.0
7/F	93	154	91	2	0	2	51	89	4	0.3	0.2
8/F	92	244	87	5	6.1	3	61	87	5	1.6	2.5
9/F	84	200	76	8	6.2	2	50	61	23	24.9	12.4
10/M	92	178	89	3	0	2	42	84	8	9.8	4.5
11/M	93	310	88	5	4.8	3	45	85	8	21.8	7.5
12/M	95	191	95	0	0	2	49	90	5	0.3	0.1
13/M	95	215	90	5	19.6	2	47	85	10	15.5	13.4
14/M	94	198	93	1	0	3	72	91	3	0	0
15/M	90	186	86	4	6.6	3	74	83	7	8.5	5.8
16/M	92	270	87	5	64.2	1	17	82	10	16.5	28.1
17/M	93	213	90	3	0	3	43	86	7	2.4	0.9
18/M	94	189	92	2	0	2	41	90	4	0.1	0
19/M	89	167	83	6	44.0	1	25	82	7	3.2	24.6
20/M	95	189	92	3	0	3	55	90	5	3.9	1.6
Women											
Mean	90.1	176	86.4	3.7	4.6	2.2	54	82	8.1	7.8	6.6
SD	8.4	49	10.0	2.3	9.4	.4	10	16.1	8.3	14.6	14.2
Men											
Mean	92.9	210	89.6	3.4	12.7	2.3	46.4	86.2	6.7	7.5	7.9
SD	2.0	43	3.5	1.9	21.8	.8	17.0	3.5	2.3	7.6	10.0
Women vs Men	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total											
Mean	91.7	194	88.2	3.5	9.0	2.3	49.9	84.3	7.4	7.6	7.3
SD	5.8	48	7.2	2.0	17.4	.6	14.6	11.0	5.7	11.0	11.8

*REM indicates rapid eye movement; Sao_2, hemoglobin saturation; RVAW, right ventricular anterior thickness; RVD, right ventricular internal dimensions; and RV-PEP/ET, right ventricular preejection period/ejection time ratio.
†Number indicates the percent of total sleep time in which there was a greater than 3% fall in Sao_2.
‡The upper limit of the normal range for RVAW and RVD are shown in parentheses.
§The upper limit of the normal range for RV-PEP/ET ratio is 0.35.

In 18 patients in whom two or more epochs of REM were monitored, the maximum fall of Sao_2 in each epoch for a given individual was reproducible. In two subjects (patients 6 and 17), repeated sleep studies were performed six and four weeks, respectively, after the initial study. For both patients, the degree of airway obstruction and hyperinflation were similar on both occasions. The maximum falls in Sao_2 in both non-REM and REM sleep were reproducible in these two patients.

Large falls in Sao_2 during REM sleep as exhibited by two women, patient 6 (22%) and patient 9 (23%) (Table 3), seem to be associated with a poor prognosis, as both patients died of respiratory and right ventricular failure within three and five months, respectively, of the sleep study. Autopsy results confirmed the presence of right ventricular hypertrophy. Left ventricular wall thickness and RVAW in patient 6 was 0.9 cm and 1.2 cm (normal, 0.3 cm), respectively. The corresponding values in patient 9 were 1.7 cm and 0.7 cm (normal, 0.3 cm), respectively. A third woman, patient 8, who had a maximum fall in Sao_2 during REM sleep of 5% (Table 3), also died of cardiorespiratory failure within two months of the sleep study, but an autopsy was not performed.

The echocardiographic data are given in Table 3. Three out of 15 patients had increased RVAW; 11 had increased right ventricular cavity size; and the RV-PEP/ET ratio was increased in eight of the 11 patients in whom it could be assessed. Eight of nine patients with a maximum fall in Sao_2 of greater than 3% during REM sleep had abnormal RV-PEP/ET ratios (Fig 2).

For the CF group as a whole, there was no significant correlation between RVAW, the RV-PEP/ET ratio and pulmonary function parameters, and the minimum waking Sao_2. Similarly, there was no significant correlation between RVAW or the RV-PEP/ET ratio and the degree or duration of desaturation during sleep.

RVAW, mm‡	RVD, mm	RV-PEP/ET§
4 (4)	25 (19)	...
...	...	...
4 (4)	19 (19)	0.31
6 (4)	23 (19)	0.57
3 (4)	20 (18)	0.34
4 (4)	24 (19)	0.38
4 (4)	24 (19)	0.41
3 (4)	15 (18)	0.49
5 (4)	26 (19)	...
3 (3)	21 (17)	...
4 (4)	19 (19)	0.39
3 (4)	29 (19)	0.48
3 (4)	32 (21)	0.45
...	...	...
4 (4)	30 (20)	0.33
4 (4)	24 (19)	0.60
...	...	...
...	...	...
...	...	...
6 (4)	18 (19)	...
...	...	...
...	...	...
...	...	...
...	...	...
...	...	...
...	...	...
...	...	...

COMMENT

Control Group

The relatively small falls in Sao_2 during sleep in the present control group are consistent with earlier reports,[17-19] but are at variance with a study of apparently normal adults that reported falls in Sao_2 of up to 29% during sleep.[20] However, this latter study included older, obese men who snored heavily, and therefore may have included subjects with early forms of the sleep apnea syndrome.[28,29] None of the subjects in the present control group were obese or snored. Furthermore, none had central apneic episodes. This is consistent with previous reports, in which periodic breathing with apneic episodes

Table 4.—Correlation Between Maximum Fall in Hemoglobin Saturation (Sao_2) During Rapid Eye Movement (REM) and Non-REM Sleep and Pulmonary Function

		REM		Non-REM	
	N	r	P	r	P
Minimum waking Sao_2, %	20	−.829	<.001	−.580	<.01
Pao_2, mm Hg	12	−.800	<.01	−.632	<.05
FVC,* % predicted	20	−.705	<.001	−.781	<.001
RV/TLC, %	20	.651	<.01	.663	<.01
FEV_1, % predicted	20	−.627	<.01	−.669	<.01
RAW, % predicted	18	.605	<.01	.597	<.01
FEF, % predicted	20	−.548	<.02	−.495	<.05

*FEV indicates forced vital capacity; RV/TLC, residual volume/total lung capacity; FEV_1, forced expiratory volume in 1 s; RAW, airways resistance; and FEF, forced expiratory flow during middle 50% of FVC.

Table 5.—Cystic Fibrosis (CF) and Control Groups Sleep Data

		Non-REM*		REM	
	Awake, Minimum Sao_2, %	Minimum Sao_2, %	Maximum Fall in Sao_2, %	Minimum Sao_2, %	Maximum Fall in Sao_2, %
CF, N = 20					
Mean	91.7	88.2	3.5	84.3	7.4
SD	5.8	7.2	2.0	11.0	5.7
Control, N = 5					
Mean	97.4	96.8	0.6	95.4	2.0
SD	0.9	0.8	0.6	1.3	0.7
Difference, significance	<.05	<.025	<.005	<.05	<.05

*REM indicates rapid eye movement; Sao_2, hemoglobin saturation.

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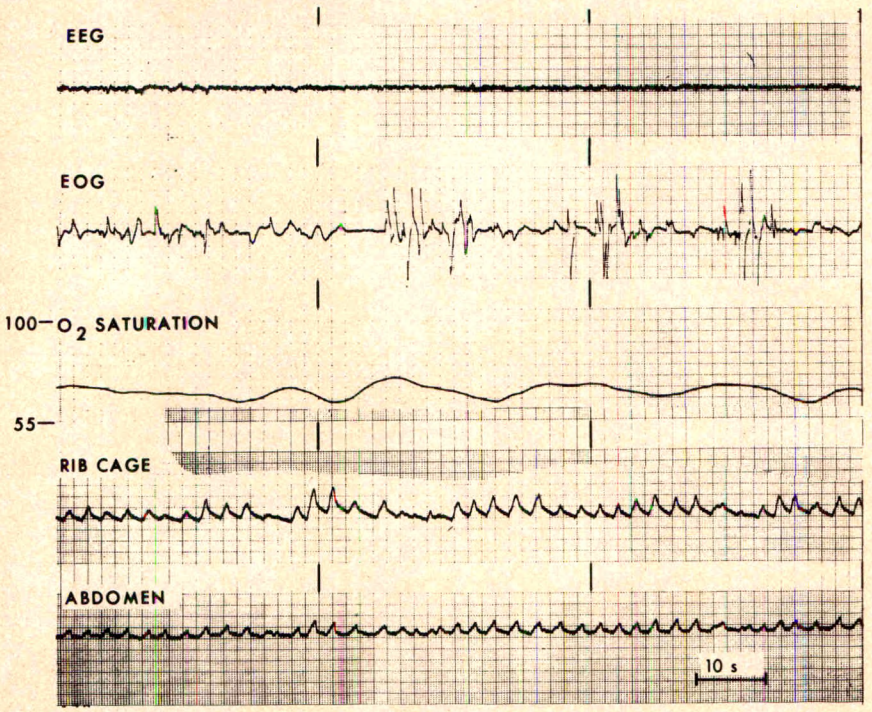
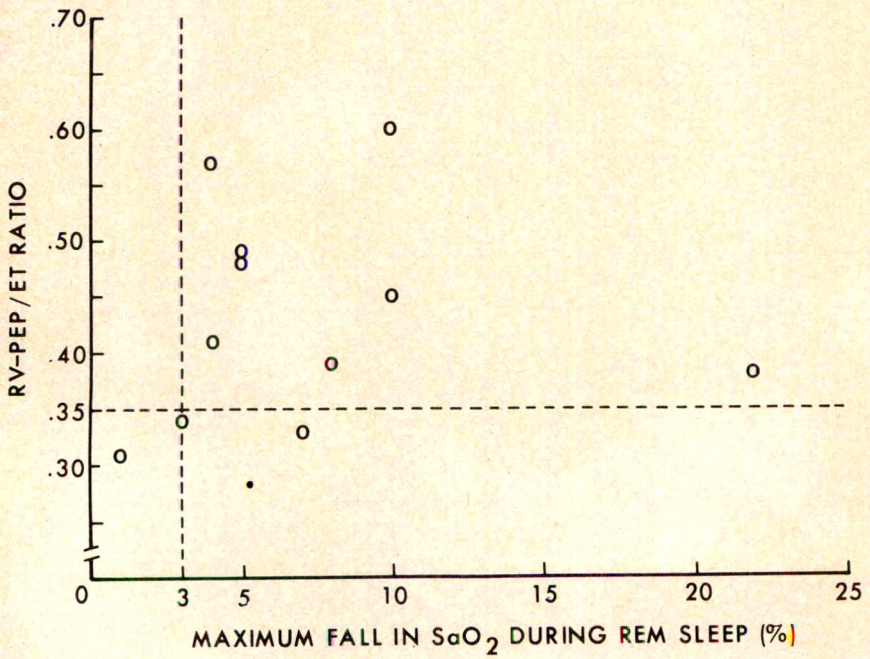


Fig 1.—Portion of rapid eye movement (REM) sleep in patient 9, whose minimum waking hemoglobin saturation (Sao_2) was 84%. After short episodes of hypoventilation associated with bursts of REM, there are falls in Sao_2, reaching values as low as 62% without any behavioral evidence of arousal response. As transition to REM sleep is not shown, fall in functional residual capacity is not apparent in this figure.

Fig 2.—Right ventricular preejection period/ejection time (RV-PEP/ET) ratio (normal, 0.35) plotted against maximum fall in hemoglobin saturation (Sao_2) during REM sleep. Upper limit of 3% fall in saturation is derived from control group.



during REM sleep was not seen in young adults,[30,31] but was frequently seen in healthy adults older than 40 years of age.[30,32]

The falls in Sao_2 values during REM sleep seems to be due to a decrease in tonic respiratory muscle activity resulting in a fall in FRC with consequent increased airway closure and increased intrapulmonary shunting.[33] This is consistent with the results of previous studies, which have demonstrated a loss of tonic activity in both the diaphragm[34] and intercostal muscles[35] during REM sleep in healthy adults. Superimposed on this were short episodes of hypoventilation, usually accompanying bursts of REM, that led to further falls in Sao_2.[33]

CF Group

In the CF group, the maximum falls in Sao_2 were seen during REM sleep. As in the control group, the desaturation was associated with short periods of hypoventilation (Fig 1) superimposed on a reduction in FRC. In none of these patients was the desaturation associated with apneic episodes or snoring. These findings are consistent with those reported in CF patients of similar mean age as the present study group.[36] However, these findings contrast with reports of adults with COLD, where the desaturation during REM sleep could not be explained by the pattern of breathing observed during this sleep stage.[37] In addition, studies in adults with COLD have described marked desaturation occurring in association with snoring,[9] as well as shorter episodes of desaturation due to hypoventilation and apnea that occurred mainly in non-REM sleep.[37] These mechanisms were not seen in the present study.

Thus, the hemoglobin desaturation during REM sleep in the CF patients seems to be due to mechanisms seen in healthy subjects of similar age. The larger falls in Sao_2 seen in the CF group compared with the control group partly reflect the fact that many of these patients had awake saturations near or on the steep portion of the oxyhemoglobin dissociation curve. Consequently, a given fall in Pao_2 would result in greater falls in Sao_2 in the CF patients as compared

with control subjects. In addition, because CF patients have an increased tendency for airway closure to develop,[38] the loss in FRC would result in a greater increase in intrapulmonary shunting as compared with control subjects.

Previous studies in the waking state have described only small shifts to the right in the oxyhemoglobin dissociation curve in CF.[39] As changes in $Paco_2$ and pH were not monitored during sleep in the present study, it is not possible to predict their effect on the position of the oxyhemoglobin dissociation curve. Nevertheless, it seems reasonable to assume that the low Sao_2 values recorded during REM sleep in many patients (Table 3) correspond to quite low Pao_2 values.

With only a single night's sleep being monitored, it is not possible to draw any firm conclusions as to the quality of sleep in these patients. However, it was apparent that some patients with severe lung disease had episodes of coughing in both non-REM and REM sleep that led to arousal and consequent sleep disturbance.

It is interesting to note that there was no significant difference between the sexes with respect to the degree of hemoglobin desaturation seen during both non-REM and REM sleep. This contrasts with the results of a recent study of apparently normal adults, in which hemoglobin desaturation was not seen in women but was frequently observed in men.[20] Furthermore, of the 54 adults with COLD in whom hemoglobin desaturation during sleep has been reported, 47 have been men.[8,9,12,37,40] This most likely reflects the higher incidence of COLD among men, as well as the tendency in men for snoring and hemoglobin desaturation during sleep to develop with increasing age.[20,29]

In the present study, the maximum falls in Sao_2 during REM and non-REM sleep correlated significantly with the severity of the lung disease (Table 4). This contrasts with one study of adults with COLD where changes in Pao_2 during sleep were not related to the degree of airways obstruction.[8] In another study of adults with COLD, the maximum falls in Sao_2 during sleep correlated with the FEV_1-vital capacity ratio, but not with other spirometric parameters, the waking Sao_2, or the waking Pao_2.[9] These differences may be due to the larger number of patients and the wider range of pulmonary function encompassed by the present study, as well as the different mechanisms that contributed to the desaturation seen in adults with COLD.[9,37]

The lack of behavioral changes consistent with an arousal response to desaturation during REM sleep is consistent with recent observations in dogs, in which a diminished arousal response to both hypoxia and hypercapnia has been demonstrated during REM sleep.[41,42] Although the diminished arousal response in the CF patients is likely to lead to less sleep disturbance, it may also mean that the patients experience more profound and more prolonged desaturation during REM sleep.

The relationship between these repeated episodes of desaturation during sleep and the echocardiographic findings is not fully known. However, there is evidence to suggest that intermittent hypoxia in experimental animals leads to sustained pulmonary hypertension and right ventricular hypertrophy. Unger and co-workers[43] have shown that acute intermittent hypoxia in dogs produces progressive increases in mean pulmonary artery pressure with successive hypoxic stimuli. These workers suggested that the intermittent nature of the hypoxic stimulus may have been important in the observed response, as continuous hypoxia was not associated with a progressive rise in mean pulmonary artery pressure. More prolonged studies in rats have shown that intermittent exposure to hypoxia alone[44] or to hypoxia and hypercapnia[45] leads to sustained pulmonary hypertension and right ventricular hypertrophy.

Recent studies in adults with the sleep apnea syndrome have demonstrated progressive increases in pulmonary artery pressure with repeated hypoxic episodes.[46] Similar studies in adults with COLD have demonstrated episodic pulmonary hypertension associated with recurrent desaturation during sleep.[11,12] It has been suggested that with time the episodic pulmonary hypertension in these patients may become sustained, leading to right ventricular hypertrophy and eventual right ventricular failure.[11-14]

In the present study, six patients had RV-PEP/ET ratios greater than 0.40 (Table 3), which has been shown to be indicative of severe pulmonary hypertension.[47] None of these patients had a waking Pao_2 of less than 50 mm Hg, which has been shown previously to indicate the presence of severe pulmonary hypertension.[3] Therefore, it is postulated that the repeated episodic desaturation seen in the CF group during sleep may be a significant etiological factor in the development and progression of cor pulmonale in these patients. It is possible that nocturnal oxygen therapy may be of value in such patients. Well-controlled trials that consider patient selection, inspired oxygen concentration, and duration of oxygen therapy will be necessary to fully define the place of such therapy in the routine management of CF.

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References

1. Royce SW: Cor pulmonale in infancy and early childhood: Report on 34 patients with special reference to the occurrence of pulmonary heart disease in cystic fibrosis of the pancreas. *Pediatrics* 8:255-274, 1951.

2. Ryland D, Reid L: The pulmonary circulation in cystic fibrosis. *Thorax* 30:285-292, 1975.

3. Siassi B, Moss AJ, Dooley RR: Clinical recognition of cor pulmonale in cystic fibrosis. *J Pediatr* 78:794-805, 1971.

4. Fink RJ, Doershuk CF, Tucker AS, et al: Pulmonary function and morbidity in adults with cystic fibrosis. *Chest* 74:643-647, 1978.

5. Moss AJ, Dooley RR, Mickey MR: Cystic fibrosis complicated by heart failure. *West J Med* 122:471-473, 1975.

6. Goldring RM, Fishman AP, Turino GM, et al: Pulmonary hypertension and cor pulmonale in cystic fibrosis of the pancreas. *J Pediatr* 65:501-524, 1964.

7. Fishman AP: Chronic cor pulmonale. *Am Rev Respir Dis* 114:775-794, 1976.

8. Koo KW, Sax DS, Snider GL: Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. *Am J Med* 58:663-670, 1975.

9. Flick MR, Block AJ: Continuous in-vivo monitoring of arterial oxygenation in chronic obstructive lung disease. *Ann Intern Med* 86:725-730, 1977.

10. Wynne JW, Block AJ, Hemenway J, et al: Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive pulmonary disease. *Chest* 73 (suppl):301-303, 1978.

11. Boysen PG, Block AJ, Wynne JW, et al: Nocturnal pulmonary hypertension in COPD, abstracted. *Chest* 74:331, 1978.

12. Douglas NK, Leggett RJE, Calverley PMA, et al: Transient hypoxaemia during sleep in chronic bronchitis and emphysema. *Lancet* 1:1-4, 1979.

13. Block AJ, Boysen PG, Wynne JW: The origins of cor pulmonale: A hypothesis. *Chest* 75:109-110, 1979.

14. Flenley DC: Clinical hypoxia: Causes, consequences and correction. *Lancet* 1:542-546, 1978.

15. Rosenthal A, Tucket CR, Williams RG, et al: Echocardiographic assessment of cor pulmonale in cystic fibrosis. *Pediatr Clin North Am* 23:327-344, 1976.

16. Allen HD, Taussig LM, Gaines JA, et al: Echocardiographic profiles of the long-term cardiac changes in cystic fibrosis. *Chest* 75:428-433, 1979.

17. Robin ED, Whaley RD, Crump CH, et al: Alveolar gas tensions, pulmonary ventilation and blood pH during physiologic sleep in normal subjects. *J Clin Invest* 37:981-989, 1958.

18. Birchfield RI, Sieker HO, Heyman A: Alterations in respiratory function during natural sleep. *J Lab Clin Med* 54:216-222, 1959.

19. Aserinsky E: Periodic respiratory pattern occurring in conjunction with eye movements during sleep. *Science* 150:763-766, 1965.

20. Block AJ, Boysen PG, Wynne JW, et al: Sleep apnea, hypopnea and oxygen desaturation in normal subjects: A strong male predominance. *N Engl J Med* 300:513-517, 1979.

21. Rechtschaffen A, Kales A: *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* National Institutes of Health publication 204, 1968, pp 1-13.

22. Weng TR, Levison H: Standards of pulmonary function in children. *Am Rev Respir Dis* 99:879-894, 1969.

23. Cooper DM, Heoppner V, Cox D, et al: Lung function in Alpha$_1$-antitrypsin heterozygotes (Pi type MZ). *Am Rev Respir Dis* 110:708-715, 1974.

24. Shwachman H, Kulczycki LL: Long-term study of 105 patients with cystic fibrosis. *Am J Dis Child* 96:6-15, 1958.

25. Epstein ML, Goldberg SJ, Allen HD, et al: Great vessel, cardiac chamber, and wall growth patterns in normal children. *Circulation* 51:1124-1129, 1975.

26. Gutgesell HP, Paguet M: *Atlas of Pediatric Echocardiography.* Hagerstown, Md, Harper & Row Publishers Inc, 1978, p 209.

27. Hirschfeld S, Meyer R, Schwartz DC: The echocardiographic assessment of pulmonary artery pressure and pulmonary vascular resistance. *Circulation* 52:642-650, 1975.

28. Block AJ, Rostand RA, Boysen PG, et al: Familial obstructive sleep apnea. *N Engl J Med* 300:506, 1979.

29. Lugasesi E, Coccagna G, Cirignotta F: Snoring and its clinical implications, in Guilleminault C, Dement WC (eds): *Sleep Apnea Syndromes.* New York, Alan R Liss, 1978, pp 13-21.

30. Webb P: Periodic breathing during sleep. *J Appl Physiol* 37:899-903, 1974.

31. Reite M, Jackson D, Cahoon RL, et al: Sleep physiology at high altitude. *Electroencephalogr Clin Neurophysiol* 38:463-471, 1975.

32. Guilleminault C, Van den Hoed J, Mitler MM: Clinical overview of the sleep apnea syndromes, in Guilleminault C, Dement WC (eds): *Sleep Apnea Syndromes.* New York, Alan R Liss, 1978, pp 1-12.

33. Muller N, Francis P, Gurwitz D, et al: Mechanism of hemoglobin desaturation during rapid eye movement sleep in normals and patients with cystic fibrosis, abstracted. *Am Rev Respir Dis* 119:338, 1979.

34. Muller N, Volgyesi G, Becker L, et al: Disphragmatic muscle tone. *J Appl Physiol* 47:279-284, 1979.

35. Tusiewicz K, Moldofsky J, Bryan AC, et al: Mechanics of the rib cage and diaphragm during sleep. *J Appl Physiol* 43:600-602, 1977.

36. Stokes DC, McBride JT, Wall MA, et al: Breathing during sleep in cystic fibrosis lung disease, abstracted. *Pediatr Res* 13:542, 1979.

37. Wynne JW, Block AJ, Hemenway J: Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease. *Am J Med* 66:573-579, 1979.

38. Mansell A, Bryan AC, Levison H: Airway closure in normal subjects and patients with cystic fibrosis, abstracted. *Pediatr Res* 5:428, 1971.

39. Rosenthal A, Khan KT, Shwachman H: Hemoglobin-oxygen equilibration in cystic fibrosis. *Pediatrics* 59:919-926, 1977.

40. Wynne JW, Block AJ, Hunt LA, et al: Disordered breathing and oxygen desaturation during daytime naps. *Johns Hopkins Med J* 143:3-7, 1978.

41. Phillipson EA, Sullivan CE, Read DJC, et al: Ventilatory and waking responses to hypoxia in sleeping dogs. *J Appl Physiol* 44:512-520, 1978.

42. Phillipson EA, Kozar LF, Rebuck AS, et al: Ventilatory and waking response to CO_2 in sleeping dogs. *Am Rev Respir Dis* 115:251-259, 1977.

43. Unger M, Atkins M, Briscoe WA, et al: Potentiation of pulmonary vasoconstrictor response with repeated intermittent hypoxia. *J Appl Physiol* 43:662-667, 1977.

44. Widimsky J, Urbanova D, Ressl J, et al: Effect of intermittent altitude hypoxia on the myocardium and lesser circulation in the rat. *Cardiovasc Res* 7:798-808, 1973.

45. Nattie EE, Bartlett DJR, Johnson K: Pulmonary hypertension and right ventricular hypertrophy caused by intermittent hypoxia and hypercapnia in the rat. *Am Rev Respir Dis* 118:653-658, 1978.

46. Tilkian AG, Guilleminault C, Schroeder J, et al: Hemodynamics in sleep induced apnea: Studies during wakefulness and sleep. *Ann Intern Med* 85:714-719, 1976.

47. Hirschfeld SS, Fleming DG, Doershuk C, et al: Echocardiographic abnormalities in patients with cystic fibrosis. *Chest* 75:351-355, 1979.

60 YEARS AGO IN THE AJDC

A Study of Pneumonia in Infancy and Childhood During Recent Epidemics

The "most virulent epidemic that spread with terrifying rapidity over two hemispheres" in the 1918 and 1919 years affected children as well as adults. It was said that children were less severely affected but mortalities over 50 per cent. are recorded from the pneumonias that commonly followed. A total of 336 pneumonias observed in children under 6 years of age during these two years at the Mount Sinai Hospital were analyzed. Of these, 288 were considered bronchopneumonias, 48 lobar pneumonias. Bronchopneumonia occurred predominantly among those under 2 years, lobar pneumonia being seen more commonly over 2 years of age. Mortality was higher with the former, 18 per cent.; 10 per cent. among lobar pneumonias. These risk figures corresponded closely to those observed previously in nonepidemic years.

Bacterial agents cultured were usually the influenzae bacillus, pneumococcus, streptococcus, or staphylococcus. Two infants with low leukocyte counts of 4,000/u mm died and differential counts with below 50 per cent. polymorphonuclears had a bad prognosis. One child with a leukocyte count of 86,000 made a rapid recovery.

The most frequent complication was otitis media (seventy-five cases). Empyema developed in seventeen cases. "Meningism" and lethargic encephalitis were infrequently observed. There was one case of pneumococcal meningitis.

Most important in treatment was hygienic care and efficient nursing. Daily milk of magnesia and enemas were routine and 10 to 20 drops of whiskey every four hours produced temporary stimulation. Dry cupping was condemned. The fretful nervous mother was excluded, keeping the patient in a sunny room with fresh air and quiet surroundings.—Henry Heiman, MD, New York (20:119-123, August 1920).

Sleep Hypoxemia in Young Adults With Cystic Fibrosis

Dennis C. Stokes, MD; John T. McBride, MD; Michael A. Wall, MD; Giuseppe Erba, MD; Denise J. Strieder, MD

• **Hypoxemia, obstructive apnea, and disordered breathing during sleep have been documented in adult patients with chronic obstructive pulmonary disease. We studied sleep, oxygen saturation, and breathing in nine patients (ages 17 to 26 years) with cystic fibrosis (CF) lung disease by means of all-night polygraphic tracings. Two had brief episodes of oxygen desaturation during rapid eye movement (REM) sleep, and one patient with severe disease had prolonged desaturation with episodic worsening associated with disordered breathing in REM sleep and with cough. No patient had apnea or any evidence of upper airway obstruction, in contrast with studies of older patients. In three patients, nocturnal coughing contributed to disruption of sleep cycles. Sleep oxygen desaturation may contribute to the development or progression of cor pulmonale in some patients with CF, but it seems to be most severe only in those with advanced disease.**

(*Am J Dis Child* 134:741-743, 1980)

Most patients with cystic fibrosis (CF) suffer from obstructive lung disease at an early age. As the lung disease progresses, they frequently have early morning fatigue, headache, and poor sleep. Many CF patients also have worsening hypoxemia in the supine position,[1] blunted sensitivity to carbon dioxide,[2] and upper airway obstruction with chronic infection and nasal polyps,[3] all of which can affect breathing during sleep.

For editorial comment, see p 733.

In adult patients with chronic obstructive pulmonary disease (COPD), arterial oxygen desaturation is known to develop in association with prolonged apneas, upper airway obstruction, or disordered breathing during sleep.[4-10] Significant nocturnal falls in arterial saturation as described in these patients could be a significant stimulus for the development of pulmonary hypertension and cor pulmonale in CF patients.

To assess the importance of respiratory disorders during sleep in the natural history of CF, we monitored sleep stage, respiration, and oxygen saturation during all-night sleep in a group of CF patients.

SUBJECTS AND METHODS

We studied eight young adults and one child with CF lung disease of varying severity. Clinical status, summarized as a Shwachman score,[11] and results of pulmonary function tests are listed in the Table. The patients had been admitted to Children's Hospital Medical Center, Boston, because of exacerbation of pulmonary symptoms without pneumothorax or hemoptysis. They were studied near the end of their hospital stay, to allow full benefit from therapy and acclimatization to the hospital. During the study, they slept in their own hospital bed in the EEG sleep laboratory. All patients were receiving antimicrobial agents directed against *Pseudomonas aeruginosa*, and three (patients 1, 5 and 7) were receiving standard doses of theophylline. Informed consent was obtained before the study as approved by the Committee on Clinical Investigation of Children's Hospital Medical Center.

Sleep was monitored[12] with a six-channel EEG tracing, oculogram, and mentalis electromyogram. Movement, cough, and other artifacts were recorded by an observer on the EEG tracing. For each minute of sleep, the tracings were classified into wakefulness, stages 1, 2, 3, or 4 of sleep, or rapid eye movement (REM) sleep. Nasal and mouth airflow were monitored with thermistors taped at the mouth and nose, and a single-lead ECG with chest electrodes. Relative directions of rib cage and abdominal motion were recorded with magnetometers.[13] Oxygen saturation was monitored continuously with an ear oximeter and averaged over one- to five-minute intervals by inspection of the tracings. Nasal and mouth flow, rib cage and abdominal motion, and ECG were reviewed minute by minute for (1) heart rate, (2) respiratory rate, (3) apneic episodes longer than 10 s, and (4) upper airway obstruction, the latter indicated by absence of air flow despite continued chest and abdominal motion.

RESULTS

Sleep

The patients were able to complete one to four sleep cycles during total study, times ranging from 3.0 to 7.3 hours (mean, 5.6 hours). On the average, they spent 12% of study time in wakefulness, 15% in sleep stage 1, 29%

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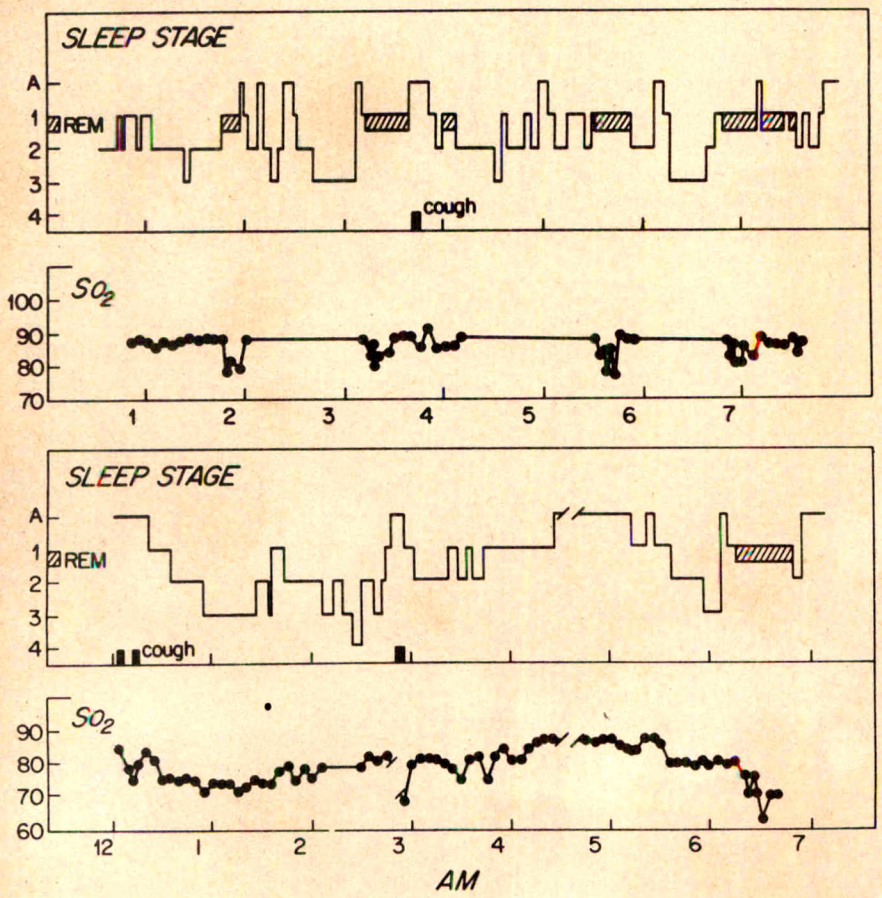
Clinical Data and Major Findings During Sleep

Patient	Age, yr/Sex	Clinical Score	Pulmonary Function: Pao_2, mm Hg	Pulmonary Function: $Paco_2$, Torr	Pulmonary Function: FEV_1*, % P	Pulmonary Function: (RV/TLC) × 100, %	Oxygen Saturation: Awake, %	Oxygen Saturation: Greatest Fall, %	Coughing With Sleep Disorganization
1	21/F	70	75	44	81	33	96	10†	–
2	19/F	75	80	42	63	42	95	3	+
3	20/M	80	65	39	52	51	96	3	–
4	12/M	60	65	42	58	42	95	4	–
5	19/M	75	69	41	34	67	91	5	±
6	20/F	60	63	38	31	45	95	2	+
7	26/M	60	62	46	20	72	88	10	±
8	24/M	50	64	44	20	66	92	8	±
9	22/M	40	47	47	17	73	87	25	+

*FEV_1 indicates forced expiratory volume in 1 s; %P, percent of predicted value; RV/TLC, body plethysmographic values of residual volume to total lung capacity ratio.

†Fall in saturation associated with bout of coughing.

Sleep stage (A indicates awake), oxygen saturation (SO_2), and prolonged coughing episodes in two subjects during all-night sleep. Top, Patient 7; SO_2 falls with each period of rapid eye movement (REM) sleep and remains stable at other times (discrete points are then omitted). Sleep cycles are regular in spite of frequent arousals. Bottom, Patient 9; SO_2 remains low throughout all-night sleep, with precipitous fall during period of REM sleep. Oximeter was disconnected temporarily at 3 and 4 AM. Coughing episode at 3 AM is associated with arousal and failure to progress to REM sleep at end of sleep cycle.



in stage 2, 12% in stage 3, 14% in stage 4, and 18% in REM sleep.

Cough

In three patients, coughing was associated with sleep disorganization. Episodes of cough during stages 1 and 2 of sleep seemed to delay progression to deeper stages of sleep. In addition, protracted coughing during transition from deep sleep to lighter stages of sleep was occasionally followed by awakening rather than by a period of REM sleep, as would have been expected.

Oxygen Saturation

Five patients with moderate to severe disease (forced expiratory volume in 1 s of 31% to 63% predicted) had minimal changes in oxygen saturation regardless of sleep stage. One patient with mild disease (patient 1) showed a single fall in saturation of 10% after a severe coughing spell during light sleep. Two patients showed significant falls in oxygen saturation during REM sleep when, in the absence of body movements, the oximeter readings were most reliable. These falls lasted from five to 17 minutes (mean, ten minutes) and occurred during more than one sleep cycle (eg, Figure, top). Patient 9 had a low saturation in all sleep stages, with worsening desaturation after coughing spells and during REM sleep (Fig-

ure, bottom). For this patient, a second all-night study was performed, during which the same pattern was observed.

Apnea and Periodic Breathing

All patients had a few brief periods of apnea without change in oxygen saturation. No episode lasted more than 10 s and in no case was upper airway obstruction observed as abdomen and rib cage motion remained in phase. However, during REM sleep, whereas abdominal motion remained constant, the magnitude of rib cage motion tended to vary periodically in 40- to 50-s cycles. Although this observation indicated fluctuation of the tidal volume, actual values of tidal volume could not be derived from the data. Rib case periodicity showed no correlation with respiratory rate, which was irregular. This pattern of breathing during REM sleep occurred in most patients and was associated with a fall of oxygen saturation in two.

Arrhythmia

No bradycardia or arrhythmia occurred. Changes in heart rate with REM sleep were seen as expected.

COMMENT

We observed that in some patients with moderate to severe CF lung disease, sleep hypoxemia develops at night. Three subjects' changes in oxygen saturation were comparable in magnitude with those reported for adult patients with COPD, but they occurred in the absence of prolonged apnea or upper airway obstruction. During REM sleep, hypoxemia was associated with disordered rib cage motion, as demonstrated by the magnetometer tracings.

Variations in the rib cage contribution to breathing in normal persons during REM sleep has been documented by Tusiewicz et al.[14] They postulated that, in patients with COPD who have a flattened and inefficient diaphragm, reduced intercostal muscle tone in REM sleep could result in reduced ventilation. In our study, because we elected not to restrict patients' freedom of movement during sleep, the magnetometers could not be calibrated to give the exact contributions of rib cage and abdomen to tidal volume. However, we observed that the greatest falls in levels of saturation occurred in the two patients (7 and 9) who had the largest residual volume to total lung capacity ratios indicative of severe air trapping and flattening of the diaphragm, consistent with Tusiewicz's hypothesis.

The role of sleep hypoxemia in the development of cor pulmonale in CF remains uncertain. Five patients with moderately severe lung disease had trivial falls in levels of oxygen saturation. Of the four who had sleep hypoxemia, two had only brief episodes. Whether such brief episodes of desaturation can lead to sustained pulmonary arterial pressure changes will require direct pressure measurements during sleep.

Both obesity and increasing age are associated with increasing occurrence and duration of sleep apnea and hypoxemia in otherwise normal adults,[15] as well as in patients with COPD or the obstructive sleep apnea syndromes.[16] Patients with CF differ from patients with nonspecific COPD in that they are young and seldom obese. This seems to protect them from obstructive apnea described in older patients. None of our patients had evidence of upper airway obstruction and only one (patient 9) had profound and recurring falls in the levels of oxygen saturation during sleep. This patient had no evidence of right ventricular failure at the time of study, yet he died five months later of cardiorespiratory insufficiency. His case raises the possibility that sleep hypoxemia related to disordered breathing without apnea or upper airway obstruction may either contribute to the rapid deterioration occasionally seen in patients with advanced CF lung disease, or may be a sign of near-terminal illness.

In addition, we observed sleep disorganization associated with nighttime cough in three patients. Cough in another patient caused transient hypoxemia. Even though response to bronchial irritation[17] and mucociliary clearance[18] are depressed during sleep, the copious secretions characteristic of CF lung disease seem capable of triggering coughing spells and disrupting the expected progression of sleep stages.

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References

1. Stokes DC, Strieder DJ, Wohl MEB, et al: Postural hypoxemia in mild cystic fibrosis lung disease. *Am Rev Respir Dis* 115(suppl):293, 1977.

2. Lwin N, Giammona ST: Ventilatory responses to inspired CO_2 in patients with cystic fibrosis. *Chest* 61:206-221, 1972.

3. Shwachman H, Kulczycki LL, Mueller HL, et al: Nasal polyposis in patients with cystic fibrosis. *Pediatrics* 30:389-401, 1962.

4. Trask CH, Cree EM: Oximeter studies on patients with chronic obstructive emphysema, awake and during sleep. *N Engl J Med* 266:639-642, 1962.

5. Koo KW, Sax DS, Snider GL: Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. *Am J Med* 58:663-670, 1975.

6. Leitch AG, Clancy LJ, Leggett JE, et al: Arterial blood gas tensions, hydrogen ion and electroencephalogram during sleep in patients with chronic ventilatory failure. *Thorax* 31:730-735, 1976.

7. Martin RJ, Orr WC, Patterson CD, et al: Respiratory function in COPD patients during different stages of sleep, abstracted. *Clin Res* 26:451A, 1978.

8. Kline NW, DeLancey DA, Giblin EC: Sleep apnea in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 117(suppl):140, 1978.

9. Douglas NJ, Leggett RJE, Calverley PMA, et al: Transient hypoxemia during sleep in chronic bronchitis and emphysema. *Lancet* 1:1-4, 1979.

10. Wynne JW, Block AJ, Hemenway J, et al: Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). *N Engl J Med* 300:513-517, 1979.

11. Shwachman H, Kulczycki LL: Long-term study of one hundred five patients with cystic fibrosis. *Am J Dis Child* 96:6-15, 1958.

12. Rechtshaffen A, Kales A: *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages in Human Subjects.* Rockville, Md, National Institutes of Health, 1968.

13. Mead J, Peterson N, Grimby G, et al: Pulmonary ventilation measured from body surface movements. *Science* 156:1383-1384, 1967.

14. Tusiewicz K, Moldofsky H, Bryan AC, et al: Mechanics of the rib cage and diaphragm during sleep. *J Appl Physiol* 43:600-602, 1977.

15. Block AJ, Hunt L, Wynne JW, et al: Sleep desaturation, apnea and hypoventilation in normal subjects. *Am Rev Respir Dis* 117(suppl):95, 1978.

16. Guilleminault C, Tilkian A, Dement WC: The sleep apnea syndromes. *Ann Rev Med* 27:465-484, 1976.

17. Phillipson EA: Control of breathing during sleep. *Am Rev Respir Dis* 118:909-939, 1978.

18. Bateman JRM, Pavia D, Clarke SW: The retention of lung secretions during the night in normal subjects. *Clin Sci Mol Med* 55:523-527, 1978.

Infectious Mononucleosis Complicated by Severe *Mycoplasma pneumoniae* Infection

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• A 14-year-old girl with infectious mononucleosis and secondary immunosuppression had severe dyspnea and cough, spiking fever, rales, and diffuse bilateral pulmonary infiltrates. The pulmonary disease progressed rapidly, necessitating empiric trials of antimicrobial agents. *Mycoplasma pneumoniae* was isolated from a lung biopsy specimen, transtracheal aspirate, and expectorated sputum, but the relatively long period required to isolate the organism delayed the microbiologic diagnosis. Serologic study of acute and convalescent serum samples confirmed the *M pneumoniae* infection. Clinical improvement was gradual, and the immunosuppression was transient. The patient's illness appeared to represent microbial synergism, with severe *M pneumoniae* infection complicating transient immunosuppression induced by infectious mononucleosis.

(*Am J Dis Child* 134:744-746, 1980)

Infectious mononucleosis is usually a self-limited lymphoproliferative disease resulting from infection with the Epstein-Barr virus. Transient suppression of immunity, especially cellular immunity, is well established during infectious mononucleosis.[1] However, reported clinical complications of this immunosuppression, especially secondary infection, are distinctly rare.[2,3]

Mycoplasma pneumoniae pneumonia is usually a self-limited respiratory infection.[4] Severe infections with *M pneumoniae* usually result from involvement of organs beyond the respiratory tract,[4] although severe respiratory tract involvement has been noted in patients with immunodeficiency syndromes.[5]

An association between infectious mononucleosis and *M pneumoniae* has been noted in a report involving two children who acquired *M pneumoniae* during convalescence from infectious mononucleosis,[2] though the immunologic status of these two patients was not reported. We describe here a patient who had infectious mononucleosis in whom suppression of cellular and humoral immunity was complicated by severe *M pneumoniae* pneumonia.

DIAGNOSTIC TECHNIQUES

Mycoplasma Isolation

Specimens included expectorated and transtracheal aspirate sputum samples, as well as tissue from lung biopsy. These were collected in sterile jars and transported to the laboratory as soon as possible. Specimens were spread over the surface of *Mycoplasma* agar plates with swabs. The swabs were then rotated and thoroughly extracted in diphasic broth. Procedures for incubation, examination of cultures, and the presumptive and confirmatory identification of *M pneumoniae* were then carried out according to published methods.[6]

Serologic Tests

The microtiter complement-fixation technique was used on serum specimens to measure antibody to *M pneumoniae*.[7] A patient's illness was considered to be associated with the potential pathogen when a fourfold change in serum titers occurred between acute and convalescent serum samples. A slide test for infectious mononucleosis heterophile antibodies was also performed.[8] The Epstein-Barr virus indirect fluorescent antibody test and the ox-cell hemolysin test were done at the Center for Disease Control, Atlanta.

REPORT OF A CASE

A 14-year-old girl was referred to the Mayo Clinic because of intermittent fever of 3½ weeks' duration. Initially, she had pharyngitis, otitis media, and cervical adenopathy. Results of a slide test for infectious mononucleosis heterophile antibodies were positive. She was given erythromycin for seven days. Ten days later, she returned with persistent fever. She was given daily injections of corticotropin for three days by a physician in her local community, presumably as treatment for fever; however, the fever recurred after four days. She was hospitalized four days for observation. An unproductive cough developed, and a roentgenogram of the chest two days before her referral showed a scant infiltrate in the left lower lobe.

Examination at our clinic disclosed a well-developed girl in no acute distress. She

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coughed intermittently and was febrile (temperature, 39.4 °C). She had lost 6.8 kg during the 2½ weeks before examination. A roentgenogram of the chest disclosed an infiltrate in the left lower lobe that appeared to be unchanged from previously (Figure, left). At admission, hemoglobin level was 9.7 g/dL; platelet count, 141,000/cu mm; and leukocyte count, 3,300/cu mm, with 50% lymphocytes (many atypical) and 45% granulocytes.

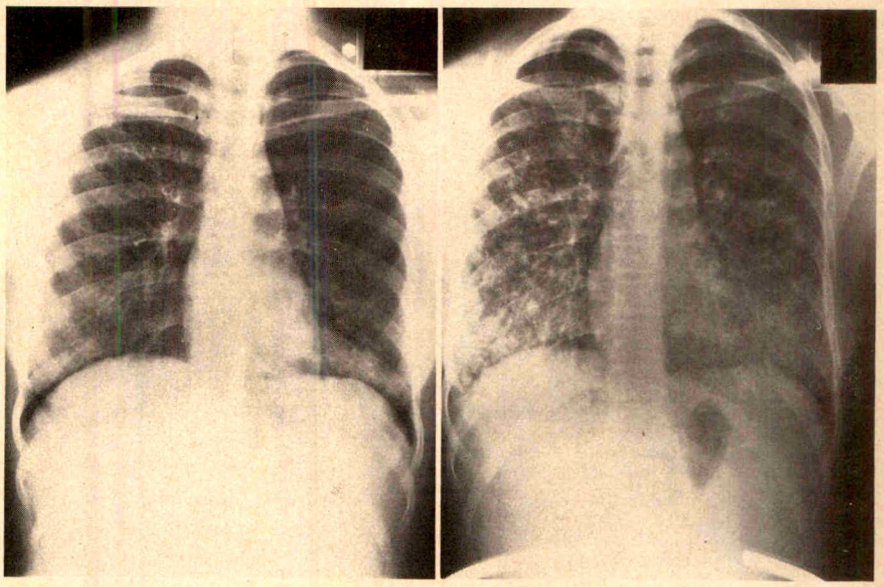
During the next three days, her cough increased in frequency and small amounts of clear, whitish sputum were produced. Cold agglutinin titer was less than 1:4; *M pneumoniae* complement-fixation titer was less than 1:2; and *Brucella* and fungal serology screen was negative. The leukocyte count was 3,900/cu mm, with 33% lymphocytes and 61% granulocytes. For the first time, rales were heard scattered in both lungs.

From day 4 through 7 after admission, her cough and sputum production increased. Fever spikes to between 40.0 and 40.6 °C began, and there was roentgenographic evidence that the infiltrates had increased dramatically (Figure, right).

Seven days after admission, a transtracheal aspirate was obtained. Gram's stain and bacterial cultures of the specimen were negative. The patient's respiratory rate was 40/min, and blood gas values on room air were as follows: Pa_{O_2}, 47 mm Hg; Pa_{CO_2}, 22 mm Hg; and pH, 7.51. She was given 40% oxygen by mask. The leukocyte count was 4,400/cu mm, with 14% lymphocytes and 83% granulocytes. IgA and IgM levels were within normal limits; however, the IgG level was 5.71 mg/mL (normal, 6.4 to 14.3 mg/mL).

Nine days after admission, the Pa_{O_2} stabilized at 60 mm Hg in 40% oxygen by mask. The leukocyte count was 3,300/cu mm, with 18% lymphocytes and 80% granulocytes. Therapy with cephalexin monohydrate, 1 g intravenously every four hours, was started. A bone marrow study showed left-shifted granulopoiesis with toxic granulation. Bone marrow cultures and stains were negative for bacteria and subsequently were negative for mycobacteria and fungi. Repeated fungal serologic studies and *M pneumoniae* titers were negative.

Eleven days after admission, the patient experienced continued deterioration, and an open lung biopsy specimen showed subacute inflammatory changes with some focal histiocytic proliferation. Silver, acid-fast, Gram's, and rhodamine stains were negative. Bacterial cultures were negative. Repeated cultures of urine, gastric aspirates, sputum, blood, and chest tube drainage were done for bacteria, fungi, mycobacteria, and *Brucella* organisms. All cultures were negative.



Chest roentgenograms. Left, At admission, infiltrate of left lower lobe. Right, Eight days later, diffuse bilateral infiltrates associated clinically with spiking fever and rales, increased sputum production, and cough with severe dyspnea.

Thirteen days after admission, with continued deterioration, the patient was given antituberculous therapy (isoniazid, rifampin, and gentamicin sulfate) after review of the lung biopsy specimen disclosed equivocal findings on the rhodamine stain. At this time, skin tests for *Candida albicans*, streptokinase, streptodornase, *Trichophyton*, and PPD were negative. The IgG level had decreased to 3.91 mg/mL, and the IgA and IgM levels remained within normal limits. The AM and PM plasma cortisone levels were above normal levels, with the expected diurnal variation.

Fourteen days after admission, the patient's condition began to improve gradually. On the 20th day after admission, she had normal T cells by E-rosette technique, but few normal B cells, as measured by surface immunoglobulin technique, were identified. Lymphocyte response to phytohemagglutinin was normal. Her condition continued to improve. On the 21st day, the transtracheal aspirate, sputum, and lung biopsy cultures were positive for *M pneumoniae*. She was given erythromycin, 500 mg every six hours, and was discharged five days later.

Serologic studies completed later on samples obtained at admission and seven and 21 days after admission confirmed the presence of antibody against Epstein-Barr virus at titers of 1:100 detected by the indirect fluorescent antibody test, along with decreasing levels (1:320 to 1:80) of ox-cell hemolysin titers. She was in good health two weeks after discharge. The IgG level had returned to normal (9.25 mg/mL). The *M pneumoniae* titer done by complement fixation was 1:32 at that time, as compared with less than 1:2 during hospitalization. She has remained in good health during the subsequent three years of follow-up.

COMMENT

The patient's illness appears to represent microbial synergism,[9] with transient immunosuppression induced by infectious mononucleosis predisposing to severe *M pneumoniae* pneumonia. Although the previous injections of corticotropin may have transiently interfered with her immunity, it is unlikely that any effect from the drug would persist with this severity for more than four weeks.[10] The patient had persistent lymphopenia and impaired cellular immunity, as evidenced by her negative skin test results for delayed hypersensitivity. She also had decreased B lymphocytes with hypogammaglobulinemia.

Many types of blood dyscrasias have been noted during infectious mononucleosis, including aplastic anemia,[11] agranulocytosis[12] and lymphopenia.[13] Hypogammaglobulinemia has been rarely found during infectious mononucleosis,[14] though the usual response is polyclonal hypergammaglobulinemia.[15] Occasional fatalities also have been reported in some families with a

genetic defect during infectious mononucleosis.[16]

Although transient immunosuppression during infectious mononucleosis is well established,[1] secondary infections are rare,[2,3] except in the presence of agranulocytosis.[12] One patient with infectious mononucleosis complicated by mixed bacterial infection has been described.[3] That patient had absent delayed hypersensitivity but normal serum immunoglobulin levels and granulocyte counts. An association between infectious mononucleosis and *M pneumoniae* also has been noted in two previously reported cases, but immunologic data were not included in that report and the *M pneumoniae* pneumonia apparently was not severe.[2] *Mycoplasma pneumoniae* pneumonia, usually a mild respiratory tract infection, is rarely fatal[4] and has been reported to be more severe in patients with immunodeficiency diseases.[5] Animal models of *M pneumoniae* infections suggest that both a cellular and a humoral immunity are involved in resistance to *M pneumoniae*.[17]

Our patient represents an uncommon complication of infectious mononucleosis from a relatively common respiratory pathogen. Two empiric trials of antibiotics failed to control the illness. The difficulty in culturing *M pneumoniae* and the prolonged period needed to obtain serologic confirmation of *M pneumoniae* infection delayed the diagnosis. This report serves to emphasize the potential for secondary infection during transient immunosuppression from infectious mononucleosis and the need to consider common but difficult to diagnose pathogens such as *M pneumoniae* in similar situations.

Nonproprietary Names and Trademarks of Drugs

Cephalexin monohydrate—*Keflex.*
Corticotropin—*Actest, Acthar, Actrope, Cortigel, Cortrophin, Depo-ACTH, Duracton.*
Gentamicin sulfate—*Garamycin.*
Rifampin—*Rifadin, Rimactane.*

References

1. Mangi RJ, Niederman JC, Kelleher JE, et al: Depression of cell-mediated immunity during acute infectious mononucleosis. *N Engl J Med* 291:1149-1153, 1974.
2. Greenstone G: Infectious mononucleosis complicated by pneumonia due to *Mycoplasma pneumoniae:* Report of two cases. *J Pediatr* 90:492, 1977.
3. Dunkle LM, Feigin RD: Infectious mononucleosis complicated by opportunistic bacterial infection. *Mo Med* 73:473-475, 1976.
4. Denny FW, Clyde WA Jr, Glezen WP: *Mycoplasma pneumoniae* disease: Clinical spectrum, pathophysiology, epidemiology, and control. *J Infect Dis* 123:74-92, 1971.
5. Foy HM, Ochs H, Davis SD, et al: *Mycoplasma pneumoniae* infections in patients with immunodeficiency syndromes: Report of four cases. *J Infect Dis* 127:388-393, 1973.
6. Smith TF: Isolation, identification and serology of *Mycoplasma pneumoniae,* in Washington JA II (ed): *Laboratory Procedures in Clinical Microbiology.* Boston, Little Brown & Co Inc, 1974, pp 205-212.
7. Sever JL: Application of a microtechnique to viral serological investigations. *J Immunol* 88:320-329, 1962.
8. Hoff G, Bauer S: A new rapid slide test for infectious mononucleosis. *JAMA* 194:351-353, 1965.
9. Mackowiak PA: Microbial synergism in human infections. *N Engl J Med* 298:21-26, 1978.
10. Butler WT, Rossen RD: Effects of corticosteroids on immunity in man: II. Alterations in serum protein components after methylprednisolone. *Transplant Proc* 5:1215-1219, 1973.
11. Mir MA, Delamore IW: Aplastic anaemia complicating infectious mononucleosis. *Scand J Haematol* 11:314-318, 1973.
12. Neel EU: Infectious mononucleosis: Death due to agranulocytosis and pneumonia. *JAMA* 236:1493-1494, 1976.
13. Bar RS, Adlard J, Thomas FB: Lymphopenic infectious mononucleosis. *Arch Intern Med* 135:334-337, 1975.
14. Provisor AJ, Iacuone JJ, Chilcote RR, et al: Acquired agammaglobulinemia after a life-threatening illness with clinical and laboratory features of infectious mononucleosis in three related male children. *N Engl J Med* 293:62-65, 1975.
15. Wollheim FA, Williams RC Jr: Studies on the macroglobulins of human serum: I. Polyclonal immunoglobulin class M (IgM) increase in infectious mononucleosis. *N Engl J Med* 274:61-67, 1966.
16. Purtilo DT, Cassel CK, Yang JPS, et al: X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). *Lancet* 1:935-941, 1975.
17. Fernald GW, Clyde WA Jr: Protective effect of vaccines in experimental *Mycoplasma pneumoniae* disease. *Infect Immun* 1:559-565, 1970.

CORRECTION

Material Deleted.—In the Marginal Comment entitled "Regression and Clinical Research," published in the June issue of the JOURNAL (134:549-552, 1980), material was left out of the first sentence of the last paragraph, page 551; it should have read as follows: "One challenge to researchers is to distinguish whether a sample is indeed from an extreme tail of a distribution."

Persistently Negative Tuberculin Reactions

Their Presence Among Children With Culture Positive for *Mycobacterium tuberculosis* (Tuberculin-Negative Tuberculosis)

Phillip Steiner, MD; Madu Rao, MD; Minerva S. Victoria, MD; Hadi Jabbar, MD; Morris Steiner, MD

• Mantoux tests were performed on 200 children with culture-proven *Mycobacterium tuberculosis* infections. A group of 28 patients initially had negative reactions to 5 TU PPD-S. Of these, 17 had had extensive or overwhelming tuberculous disease at the time of admission, seven of whom reacted to 250 TU PPD; after a course of chemotherapy, all the survivors had positive reactions to 5 TU PPD-S. The 11 with less severe disease had negative reactions to 5 TU PPD-S and 250 TU PPD, as well as to PPD-A/B/G; in only two could a ready explanation be found for the negative reactor state. In general, a small number of children without life-threatening forms of tuberculosis may have persistently negative tuberculin reactions without any apparent cause. In such cases, other criteria for diagnosis must be relied on, such as lymphocyte transformation, culture, and biopsy.

(*Am J Dis Child* 134:747-750, 1980)

The tuberculin test remains the single most valuable test in the detection of tuberculosis both diagnostically and epidemiologically. Standard pediatrics textbooks list the efficacy of 5 TU PPD as 99% in the detection of active tuberculosis in children.[1,2] Recent studies in adults have indicated that this test is not as sensitive an index of infection as previously thought.[3-6] In a recent report by Rooney and co-workers, 21 of 100 adults with culture-proven tuberculosis had negative reactions to 5 TU PPD-T on admission to the hospital.[6] Most of these patients were seriously ill, and had protein depletion. Two weeks after initiation of antituberculous therapy and proper nutrition, only 5% had negative reactions. Of these, one had Hodgkin's disease, one leukemia, and one 80-year-old patient died four weeks after a second negative Mantoux test result. Only three did not suffer from any maladies that are known to alter delayed hypersensitivity, and these patients all recovered.

Tuberculin reactions can be depressed or absent in children who are critically ill with extensive disease; in those receiving corticosteroids or immunosuppressive therapy; after the administration of some live-virus vaccines; after certain viral diseases, such as measles; in patients with diseases that interfere with immunity; and during the incubation period of primary tuberculous infection. In addition, errors in technique of administration, the use of an inactive tuberculin solution, and errors in the interpretation of the test may also result in a false-negative tuberculin test result.[7]

To our knowledge, no studies are available of tuberculin skin reactivity in culture-proven tuberculosis in children in whom none of these factors were present. We performed a study of the number of patients with initially negative tuberculin reactions among 200 children with culture-proven tuberculosis, their clinical characteristics, and the number who had

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Table 1.—Clinical Characteristics of Patients With Persistently Negative Reactions to 5 TU PPD-S

Case	Age, yr/mo	Sex	Clinical Features	No. of Skin Tests PPD-S 5 TU*	Period of Observation	Diagnosis
1	2/10	M	Fever, pleural effusion, hilar adenopathy; contact with tuberculosis; culture of pleural fluid grew *Mycobacterium tuberculosis*	8	10 mo	Hilar adenopathy, pleural effusion
2	1/0	M	Fever, pleural effusion, right upper lobe infiltrate; contact with tuberculosis; culture of pleural fluid grew *M tuberculosis*	4	4 mo	Primary pulmonary tuberculosis, pleural effusion
3	2/6	M	Fever, vomiting, cough, pleural effusion, left lower lobe infiltrate; contact with tuberculosis; culture of pleural fluid grew *M tuberculosis*	6	3 yr	Primary pulmonary tuberculosis, pleural effusion
4	3/0	M	Fever, cough, right lower lobe infiltrate; contact with tuberculosis; culture of gastric washings grew *M tuberculosis*	8	4 yr	Primary pulmonary tuberculosis
5	4/0	M	Fever, vomiting, cough, right middle lobe infiltrate; contact with tuberculosis; culture of gastric washings grew *M tuberculosis*	4	3 mo	Primary pulmonary tuberculosis
6	1/0	M	Fever, persistent right lower lobe infiltrate, no history of contact; culture of gastric washings grew *M tuberculosis*	5	3 mo	Primary pulmonary tuberculosis
7	0/3	F	Fever, cough, right middle lobe infiltrate; contact with tuberculosis; culture of gastric washings grew *M tuberculosis*	7	10 mo	Primary pulmonary tuberculosis
8	2/10	M	Fever, persistent right middle lobe infiltrate; no contact with tuberculosis; culture of gastric washings grew *M tuberculosis*	6	6 mo	Primary pulmonary tuberculosis
9	6/12	M	Heavy exposure to father who had extensive cavitary tuberculosis; culture of gastric washings grew *M tuberculosis*	8	4 yr	No demonstrable disease
10	9/0	M	History of exposure to tuberculosis, mass in superior mediastinum; culture of gastric washings grew *M tuberculosis*	6	2 yr	Leukemia
11	9/0	M	Extensive bilateral pulmonary infiltrates, fever, hepatomegaly, hilar adenopathy; culture of gastric washings grew *M tuberculosis* twice; Kveim test biopsy specimen showed noncaseating granuloma	10	2 yr	Sarcoidosis

*All patients reacted negatively to 250 TU PPD and PPD-A/B/G.

persistently negative reactions after recovery.

SUBJECTS AND METHODS

The patient group comprised 200 children, ranging in age from 1 month to 14 years, from whom strains of *Mycobacterium tuberculosis* were isolated on culture. They received treatment at the State University Hospital-Downstate Medical Center and Kings County Hospital Center, New York, during the years 1965 through 1974.

Tuberculin Tests

All children were tested with 5 TU PPD-S. Repeat tests were performed on those with negative reactions with 5 TU PPD-S, 250 TU PPD, and the nontuberculous mycobacterial antigens PPD-A/B/G. All tuberculin except the 250 TU were originally obtained from Lydia B. Edwards, MD, of the US Public Health Service (USPHS), and later from the Communicable Disease Center, Atlanta. The tuberculin material obtained from the USPHS was prepared in dilutions of 0.0001 mg/0.1 mL by the addition of buffered diluent to lyophylized PPD, and were said to retain their potency for nine months after the initial dilution.[8] The potency of the 5 TU PPD-S solutions used was confirmed by the fact that strongly positive reactions were obtained from other children tested with the same material at the same time the patients with tuberculin-negative reactions were tested.

After 1969, PPD solutions stabilized with sorbitan polyoxyalkalene derivative (Tween) were used, except for the 250 TU PPD, which was commercially obtained and freshly diluted for each test. The tests were performed intradermally in the forearm of the patient by the pediatric chest fellows and read by them at 48 hours. An area of 10 mm or more of induration was considered to be a positive reaction. Areas of 5 to 9 mm were classified as weak or doubtful reactions and 0 to 4 mm were considered to be negative reactions. Repeated tests on the patients with negative reactions were done with 5 TU PPD-S at intervals of one month until the time of discharge. Tests were repeated in some patients after discharge from the hospital in the pediatric chest clinic for as long as four years after performance of the initial tests. All children were given treatment with standard chemotherapy. Treatment was begun immediately, or soon after admission, on all patients with a positive tuberculin test and on those who had life-threatening disease, even if they had negative reactions. Treatment was delayed for seven of the nine patients with persistently negative reactions who had primary pulmonary infection, until the presence of tuberculosis was confirmed by culture (four to six weeks). The other two patients (Table 1, cases 9 and 10) were given treatment shortly after admission.

Laboratory Methods

The techniques for the isolation, identification, and susceptibility testing of *M tuberculosis* have been previously described.[9]

Table 2.—Results of Skin Testing on Admission and Discharge Among 200 Children With Positive Cultures For *Mycobacterium Tuberculosis*

Skin Reactivity Induration, mm	No. of Patients Tested (%)			
	Initial Tests		Final Tests	
	5 TU PPD-S	250 TU PPD-S*	5 TU PPD-S	250 PPD-S*
0-4	28(14.0)	21(75.0)	11(5.5)	11(100)
5-9	9(4.5)	0	5(2.5)	0
> 10	163(81.5)	7(25.0)	182(92.0)	0
Total	**200**(100)	**28**(100)	**198**(100)†	**11**(100)

*Only negative reactors to 5 TU were tested with 250 TU PPD. All were negative reactors to 5 TU PPD A/B/G.

†Two patients (initial negative reactors) with meningitis died at 12 and 21 days, respectively.

Table 3.—Clinical Characteristics of Initially Negative Reactors to 5 TU PPD-S Who Became Positive Reactors During Treatment

Case	Age, yr/mo	Sex	History of Tuberculosis Contact	mm Induration			Diagnosis
				PPD-S 5 TU	PPD-S 250 TU	PPD A/B/G	
1	3/0	F	—	0	0	0	Meningitis
2	10/0	F	+	0	0	0	Miliary, meningitis
3	0/4	M	+	0	0	0	Miliary, meningitis
4	5/0	M	+	0	27	0	Meningitis
5	1/6	M	+	0	15	0	Meningitis
6	2/0	M	—	0	0	0	Meningitis
7	7/0	M	+	0	28	0	Meningitis
8	1/6	M	+	0	40	0	Meningitis
9	2/0	M	+	0	25	0	Meningitis
10	5/0	M	+	0	15	0	Miliary, tuberculoma
11	0/1	M	+	0	0	0	Congenital tuberculosis
12	2/0	M	+	0	12	0	Chronic hematogenous tuberculosis
13	13/0	M	—	0	0	0	Extensive cavitary tuberculosis
14	9/0	M	—	0	0	0	Pott's disease
15	2/0	F	—	0	0	0	Extensive pulmonary tuberculosis
16*	4/0	F	+	0	0	0	Meningitis: died 12 days after admission
17*	3/0	F	+	0	0	0	Meningitis: died of disseminated intravascular coagulopathy 3 wk after admission

*Died; not retested.

RESULTS

There were 200 children, 108 boys and 92 girls, from whom *M tuberculosis* was isolated from sputum, gastric washings, spinal fluid, pleural fluid, or lymph nodes. Of these, 141 had primary pulmonary tuberculosis, of whom two had associated serious diseases, one with leukemia and the other with sarcoidosis. The remaining 59 patients had serious or life-threatening forms of tuberculosis, ie, meningitis, miliary tuberculosis, or bone tuberculosis, and two had congenital tuberculosis. All patients in the study were similar with regard to age, race, history of exposure to tuberculosis, and socioeconomic status.

On admission to the hospital, 163 (81.5%) had strong, positive reactions to 5 TU PPD-S, nine (4.5%) had weak or doubtful reactions (5 to 9 mm), and 28 (14%) had negative reactions. Seven of the 28 with negative reactions reacted to 250 TU PPD, but not to 5 TU PPD-A/B/G. On retesting with 5 TU PPD-S from one to six months after initiation of therapy, 182 (92%) had strong reactions and five (2.5%) weak reactions. Eleven (5.5%) had persistently negative reactions to 5 TU PPD-S, 250 TU PPD, and PPD-A/B/G (Table 2).

The characteristics of the patients with persistently negative reactions are given in Table 1. In Table 3 are given the characteristics of those patients who initially had negative reactions, but who then had positive reactions to 5 TU PPD-S after initiation of therapy.

COMMENT

A surprisingly large percent of the children (5.5%) with culture-proven tuberculosis had persistently negative tuberculin reactions. All but two of these children (Table 1, cases 10 and 11) did not have overwhelming disease, were well nourished, and had no apparent clinical evidence of an imunological deficiency. There were no demonstrable clinical differences between those with positive or negative reactions with primary tuberculosis with respect to age, onset of illness, symptoms, or socioeconomic status. There was a difference in the onset of treatment between these two groups, in that treatment was delayed in all but two patients in the group with persistently negative reactions until the diagnosis was established by culture (four to six weeks). Thus, early initiation of treatment was not a factor in the group with persistently negative reactions. Houk et al reported that those with positive reactions, if treated soon after exposure to tuberculosis, will revert to a tuberculin-negative state.[10] However, none of the patients in his report had demonstrable disease, as did eight of the nine of our patients who had persistently negative tuberculin reactions (Table 1, cases 1 through 9). The two other patients in this group, cases 10 and 11, had adequate explanation for their tuberculin-negative states; one

had leukemia and the other sarcoidosis. Excluding these two cases, the persistently negative reaction rate for all 200 culture-proven cases of tuberculosis was 4.5%. The persistently negative reaction rate for the 139 positive-culture patients with primary tuberculosis and no complicating disease was 6.5%. An additional 303 patients, not included in this study, received treatment at our institution for primary pulmonary tuberculosis during the study period. All had negative cultures and the diagnosis was based on a history and chest roentgenogram compatible with primary pulmonary tuberculosis, plus a positive Mantoux test.

It is of interest that all of the patients with initially negative reactions who reverted to a positive reaction state came from the group of patients who had serious or life-threatening forms of tuberculosis, whereas all those with persistantly negative reactions had primary pulmonary tuberculosis. From our data, no explanation can be given for this finding. One can speculate that since the more serious forms of diseaes occur after a primary infection, the disease process has been present for a longer time and that those patients were more heavily infected. Both of these factors might provide a greater antigenic stimulus to the host, which becomes manifested by positive skin reactivity during or after recovery. It is also possible that these patients had initially positive reactions who reverted to a negative reaction state with the onset of serious or overwhelming disease and again had positive reactions on recovery. In contrast, those with persistently negative reactions never manifested positive skin reactivity either before or after treatment.

These findings indicate that the Mantoux test cannot be relied on as the sole criterion for the diagnosis of tuberculosis, as a small but significant number of children with culture-proven tuberculosis (4.5%) who do not have severe or overwhelming disease and whose immune system is not apparently compromised will consistently fail to react to tuberculin. In such instances, other diagnostic procedures, such as lymphocyte transformation,[11] culture, and biopsy, may have to be used to establish the diagnosis.

It is highly improbable that our results are due to improper techniques or faulty test materials, as all tests were performed and read by trained fellows in pediatric chest disease.

Through 1969, diluted, nonstabilized tuberculin was used. This material has been reported to be unstable and in some instances to have been responsible for false-negative tuberculin tests.[12] The question of potency and stability of the tuberculin solutions used was raised when our first culture-positive, tuberculin-negative patient was encountered in 1965 (Table 1, case 7). Potency of the PPD-S was checked by testing several known positive reactors, and was found to give strong positive reactions. The potency of all the PPD-S solutions used to test the other culture-positive, tuberculin-negative patients was similarly assured by testing known positive reactors. Secondly, all patients with persistently negative tuberculin reactions had four or more tests, and a different vial of PPD-S was used for each test. These multiple tests with different vials of PPD-S virtually eliminated the possibility of faulty technique.

It is of interest to note the significant predominance of boys among the persistently negative reactor group (Table 1). Only one of 11 patients was a girl. The reason for the predominance of boys in this group is not apparent.

References

1. Lincoln EM, Sewell EM: Tuberculosis, in Krugman S, Ward R (eds): *Infectious Diseases of Children and Adults*, ed 6. St Louis, CV Mosby Co, 1977, pp 389-450.
2. Kendig RJ Jr: Tuberculosis, in Kendig RJ Jr (ed): *Pulmonary Disorders*, ed 3. Philadelphia, WB Saunders Co, 1977, vol 1, pp 787-838.
3. Holden M, Dubin MR, Diamond PH: Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. *N Engl J Med* 285:1506-1509, 1971.
4. Kent DC, Schwartz R: Active pulmonary tuberculosis with negative tuberculin skin reactions. *Am Rev Respir Dis* 95:411-418, 1967.
5. Hyde L: Clinical significance of the tuberculin skin test. *Am Rev Respir Dis* 105:453-454, 1972.
6. Rooney JJ, Cracco JA, Kramer S, et al: Further observations on tuberculin reactions in active tuberculosis. *Am J Med* 60:517-522, 1976.
7. *Diagnostic Standards and Classification of Tuberculosis and Other Mycobacterial Diseases, Supplement: The Tuberculin Skin Test*. New York, American Lung Association, 1974, pp 3-15.
8. Edwards LB, Cross RW, Hopwood M: Effect of duration of storage on the potency of dilutions of PPD antigens. *Tubercule* 44:153-161, 1963.
9. Steiner M, Coscio A: Primary tuberculosis in children: I. Incidence of primary drug-resistant disease in 332 children observed between the years 1961 and 1964 at the Kings County Medical Center of Brooklyn. *N Engl J Med* 274:755-759, 1966.
10. Houk VN, Kent DC, Sorensen K, et al: The eradication of tuberculosis infection by isoniazid chemoprophylaxis. *Arch Environ Health* 16:46-50, 1968.
11. Gupta MS, Verma IC, Ghai OP: In vitro lymphoblastoid transformation in the presence of tuberculin as a diagnostic aid in tuberculous meningoencephalitis. *Am Rev Respir Dis* 110:592-597, 1974.
12. Landi S, Held HR, Tseng MC: Disparity of potency between stabilized and nonstabilized dilute tuberculin solutions. *Am Rev Respir Dis* 104:385-393, 1971.

Ankyloblepharon Filiforme Adnatum

Congenital Eyelid-Band Syndromes

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• Three infants had congenital eyelid bands, ankyloblepharon filiforme adnatum (AFA), in association with cleft lip and palate. A review of the literature of all previously reported cases of AFA was performed and a new classification of the various clinical types of AFA is proposed. This new classification should aid in genetic counseling.

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Ankyloblepharon filiforme adnatum (AFA) is a rare congenital anomaly that was first described by von Hasner in 1881.[1] The term describes the pathology of fine strands of tissue joining the upper and lower eyelids. The abnormality has been reported as an isolated finding, in association with other anomalies and as part of defined syndromes. We wish to report three additional cases of AFA that should further assist physicians in defining the teratogenetic implications of this entity. In addition, an attempt will be made to categorize the various conditions wherein AFA occurs so as to provide a rational guide for genetic counseling.

REPORT OF CASES

Case 1.—A 3,650-g first born male infant was born after an uncomplicated full-term pregnancy to unrelated healthy Sephardic Jewish parents. The maternal grandfather had a cleft lip. Physical examination showed complete right cleft lip and palate (Fig 1) and bilateral AFA (Fig 2). No other physical abnormalities were noted. Analysis of the chromosomes of the father and the infant showed a similar karyotype of 46 chromosomes with balanced reciprocal translocation—46, XY, t (4:16). The mother had a normal female karyotype. At the age of 3 days, the AFA was severed and one month later the cleft lip was repaired. Follow-up examination of the infant at age 6 months showed a normally grown infant with appropriate development.

Case 2.—A 3,300-g female infant was born after an uncomplicated pregnancy to unrelated Ashkenazic Jewish parents. The parents' phenotype was normal, except for a short upper lip in the father. The infant had a total bilateral cleft lip and palate and bilateral AFA. The AFA was released at age 3 months.

Case 3.—Four years later, a male sibling was born after an uncomplicated full-term pregnancy to the parents of case 2. The infant had a bilateral cleft lip and palate, bilateral AFA (Fig 3 and 4), and clinodactyly of both fifth fingers. The karyotype was normal. The AFA was released at age 3 months. Follow-up examination of the child at age 6 years showed no abnormalities.

A third pregnancy ended in an induced abortion during the first trimester. No pathological examination of the fetus was performed.

COMMENT

Normal fusion of the eyelids is purely epithelial, begins during the ninth week of gestation, and is complete by the 11th week.[2-3] In our cases, however, as in others,[1-3] the filiforme bands consisted of a core of vascularized connective tissue covered by epithelium. Thus, it is clear that the bands reflect a defect in the fusion process and not in the separation that occurs between the fifth and seventh months of gestation. Although the teratogenetic cause of this defect is not clear, it is not surprising that anomalies of the lips and palate occur with great frequency in association with AFA, as these structures begin their develop-

Fig 1.—Cleft palate and cleft lip in male infant of family 1.

Table 1.—Ankyloblepharon Filiforme Adnatum Types

Type	Associated Anomalies	•Genetics
1	None	Sporadic
2	CNS and/or cardiac	Sporadic
3	Ectodermal syndromes	Autosomal-dominant; variable expressivity
4	Cleft lip and/or palate	Autosomal-dominant; variable expressivity

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Fig 2.—Bilateral ankyloblepharon filiforme adnatum in male infant of family 1. Note bands in center of eyelids.

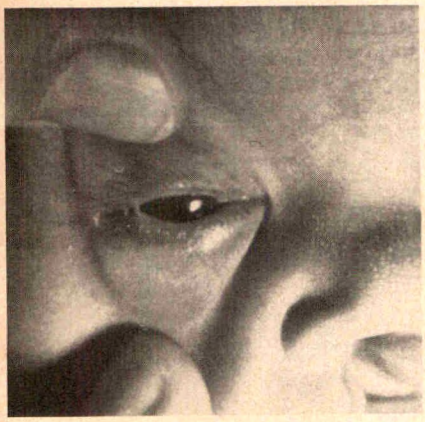

Fig 3.—Ankyloblepharon filiforme adnatum in right eye of male infant of family 2. Note two bands on lateral aspect of eyelids.

Fig 4.—Ankyloblepharon filiforme adnatum in left eye of male infant of family 2. Note single band on lateral aspect of eyelids.

ment in the seventh week of fetal life and are complete by the ninth week of gestation. The AFA themselves are of minor clinical importance because they pose little functional or therapeutic problems. No increased incidence of refractive errors, strabismus, or amblyopia has been reported. The bands frequently resolve spontaneously after a few months[4] or may be released by a simple operative procedure. The major practical importance of this anomaly is that when it occurs, it should alert the physician to the presence of other anomalies and to the possibility that a particular genetic pattern may be present.

A review of the literature indicates that the infants with AFA can be classified into four separate patterns of presentation (Table 1). Type 1 includes cases in which no associated defect in either the proband or the family are noted. These occur sporadically in no particular genetic pattern.[5-7] Type 2 includes cases in which AFA is associated with severe life-threatening cardiac or CNS defects. These reports are of sporadic cases without any familial pattern.[8-10] Type

Table 2.—Type 4 Ankyloblepharon Filiforme Adnatum: Cleft Lip and Palate Associated*

Source, yr	No. of Cases	Anomalies	Family and Genetics
Lohlein,[14] 1930	1	AFA, cleft lip	Unknown
Test and Falls,[15] 1947; Van der Woode,[16] 1954	1	AFA, fistula labii inferioris	Eight with cleft lip and/or palate in 5 generations, autosomal-dominant, variable expressivity
Khanna,[17] 1957	1	AFA, cleft lip and palate	Sister with AFA
Lemtis and Neubauer,[18] 1959	1	AFA	Paternal uncle and 2 of his 3 sons, cleft lip and palate; probably recessive
Long and Blandord,[19] 1962	1	AFA, bilateral complete cleft lip and palate	Paternal aunt with cleft lip and palate
Gupta and Saxena,[20] 1962	2	AFA, cleft lip	Siblings
Pahwa and Sud,[21] 1966	1	AFA, cleft lip and palate	Unknown
Sood et al,[22] 1968	1	AFA, complete cleft lip and palate	Maternal aunt with cleft lip and palate
Ehlers and Jensen,[23] 1970	1	AFA, complete cleft lip and palate	Father and maternal aunt with cleft lip and palate; grandfather with cleft lip
Present study 1979	1	AFA, cleft lip and palate	Maternal grandfather with cleft lip; proband and father balanced chromosomal translocation
	2	AFA, bilateral complete cleft lip and palate	Siblings with normal karyotype; father with short upper lip; autosomal-dominant variable expressivity

*AFA indicates ankyloblepharon filiforme adnatum.

3 AFA occurs in association with ectodermal syndromes, such as the popliteal pterygium syndrome[11-12] and the ankyloblepharon ectodermal defect and clefting syndrome.[13] These patients have an autosomal-dominant pattern with variable degrees of expressivity.

Of greatest interest to the pediatrician is type 4 (Table 2) AFA.[14-23] In this type, cleft lip and palate defects have been noted either in the proband or in the extended family. Our three cases, no doubt, fit into this group and illustrate the problem of simple genetic definition. The majority of such infants described in the literature occur in families with definite propensity to cleft lip and palate. In some families, an autosomal-dominant gene seems to be present, whereas in others either an autosomal-recessive pattern predominates or a multifactorial cause is likely. What is relevant to the pediatrician, however, is the fact that the presence of a cleft lip or palate in one member of the family and AFA in another should alert one to the increased possibility of additional cases of cleft lip and palate appearing in subsequent children.

Chromosomal studies have not been previously reported with AFA. In the first case, a balanced translocation (46, XY, t [4:16]) was found in the proband and the father. Since the mother had a normal karyotype and familial cleft lip occurred in the maternal grandfather, no association of AFA with this translocation anomaly is likely. This is further supported by the normal karyotype pattern in the third case.

Our attempt to categorize the AFA syndrome into four types is no doubt open to debate. However, until further cases are reported and more detailed family studies are performed, a clearer definition of the genetics is unlikely. Until such time, the appearance of AFA in an infant should alert the clinician to the potential birth in the same family of other infants with associated anomalies and our guide should assist him in the counseling of such families.

Professor J. Chemke referred family 2 for study, and Ada Roseman, MD, performed the cytogenetic studies.

References

1. Von Hasner: Ankyloblepharon filiforme adnatum. *Z F Heilk* 2:429, 1881.
2. Mann I: *The Development of the Human Eye*, ed 3. London, British Medical Association, 1964, pp 259-269.
3. Duke-Elder S: *System of Ophthalmology: Embryology*. London, Henry Kimpton, 1963, vol 3, pp 231-245.
4. Howe J, Harcourt B: Ankyloblepharon filiforme adnatum affecting identical twins. *Br J Ophthalmol* 58:630-632, 1974.
5. Bunzel R: Ankyloblepharon filiforme adnatum. *Prager Med Wchnschr* 22:441-442, 1897.
6. Reis W: Ankyloblepharon filiforme adnatum. *Arch F Augenh* 58:283-289, 1907.
7. Mattson R: Ankyloblepharon filiforme adnatum. *Acta Ophthalmol* 28:223-227, 1950.
8. Lobstein A, Haarscher A: Ankyloblepharon filiforme congenital et malformation cardiaque associée. *Bull Soc Fr Ophthalmol* 2:128-130, 1953.
9. Rogers JW: Ankyloblepharon filiforme adnatum. *Arch Ophthalmol* 65:114-117, 1961.
10. Kazarian EL, Goldstein P: Ankyloblepharon filiforme adnatum with hydrocephalus, meningomyelocele and imperforate anus. *Am J Ophthalmol* 84:355-357, 1977.
11. Kind HP: Popliteales pterygiumsyndrom. *Helv Pediatr Acta* 25:508-515, 1970.
12. Pfeiffer RA, Tunte W, Und Reinken M: Das kniepterygiumsyndrom. *Z Kinderheilk* 108:103-115, 1970.
13. Hay RJ, Wells RS: The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: An autosomal dominant condition. *Br J Dermatol* 94:277-289, 1976.
14. Lohlein W: Kurzes handbuch der ophthalmologie. Berlin, Springer Verlag, 1930, pp 252-253.
15. Test AR, Falls HF: Dominant inheritance of cleft lip and palate in five generations. *J Oral Surg* 5:292-297, 1947.
16. Van Der Woode A: Fistula labii inferioris congenita and its association with cleft lip and palate. *Am J Hum Genet* 6:244-255, 1954.
17. Khanna VN: Ankyloblepharon filiforme adnatum. *Am J Ophthalmol* 43:774-777, 1957.
18. Lemtis H, Neubauer H: Ankyloblepharon filiforme et membraniforme adnatum. *Klin Mbl Augenheilk* 135:510-515, 1959.
19. Long JC, Blandord SE: Ankyloblepharon filiforme adnatum with cleft lip and palate. *Am J Ophthalmol* 53:126-129, 1962.
20. Gupta SP, Saxena RC: Ankyloblepharon filiforme adnatum. *J All-India Ophthalmol Soc* 10:19-21, 1962.
21. Pahwa JH, Sud SD: Ankyloblepharon filiforme adnatum. *Orient Arch Ophthalmol* 4:170-173, 1966.
22. Sood NN, Agrawal TP, Ratnaraj A: Ankyloblepharon filiforme adnatum with cleft lip and palate. *J Pediatr Ophthalmol* 5:30-32, 1968.
23. Ehlers N, Jensen IK: Ankyloblepharon filiforme congenitum associated with harelip and cleft palate. *Acta Ophthalmol* 48:465-467, 1970.

Group B Streptococcal Disease

Its Diagnosis With the Use of Antigen Detection, Gram's Stain, and the Presence of Apnea, Hypotension

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• Antigen detection was found to be a rapid and useful technique in diagnosing group B streptococcal (GBS) infections. Of the two techniques described, latex agglutination was more sensitive than countercurrent immunoelectrophoresis. Concentrated urine was the best body fluid to test with 100% containing antigen. Though no false-positive reactions were noted, this is a potential problem. Gram-positive cocci in the gastric aspirate were associated with severe systemic infections with these organisms in almost half of the neonates with clinical signs of infection or respiratory distress syndrome (RDS). There was only a 4% infection rate in clinically similar neonates without Gram-positive cocci in the gastric aspirates. Apnea and/or hypotension was seen commonly in both early onset GBS pneumonia and RDS, making this finding alone of little clinical use.

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Clinically, it is difficult to distinguish between early onset (≤ 7 days of life) group B streptococcal (GBS) pneumonia and respiratory distress syndrome (RDS).[1-2] Similarly, it is difficult to distinguish between GBS infections and infections caused by other organisms. A number of clinical and laboratory characteristics have been suggested as being useful in these situations. In studies with a small number of cases, the three characteristics reported to be more suggestive of early onset GBS pneumonia than RDS were the presence of GBS antigen in body fluids,[3-7] Gram-positive cocci in the gastric aspirate,[3,8] and the presence of apnea and/or shock in the first 24 hours of life.[8,9] The purpose of this study is to test the usefulness of these findings in identifying neonates with early onset GBS pneumonia vs RDS, and also to describe a latex agglutination (LA) test and countercurrent immunoelectrophoresis (CIE) test that may be used to detect GBS antigen in body fluids in early onset and late onset GBS disease.

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METHODS

Three studies were performed to evaluate the usefulness of antigen detection (study 1), Gram-positive cocci in the gastric aspirate (study 2), and the presence of apnea and/or hypotension (study 3 [Fig 1 to 3]) as indicators of GBS infections. The studies were performed simultaneously.

Patient Population

The study populations were the neonates hospitalized at the Wake County Medical Center, Raleigh, NC, and the North Carolina Memorial Hospital, Chapel Hill, between January 1976 and December 1978. During this time, 19 neonates had early onset GBS pneumonia. Of these, 16 had available body fluids tested for GBS antigen (study 1), 13 had gastric aspirate Gram's stains and cultures (study 2), and all 19 were monitored for apneic spells and hypotension (study 3).

Eight neonates had other types of early onset GBS disease other than pneumonia. Seven had body fluids available for antigen

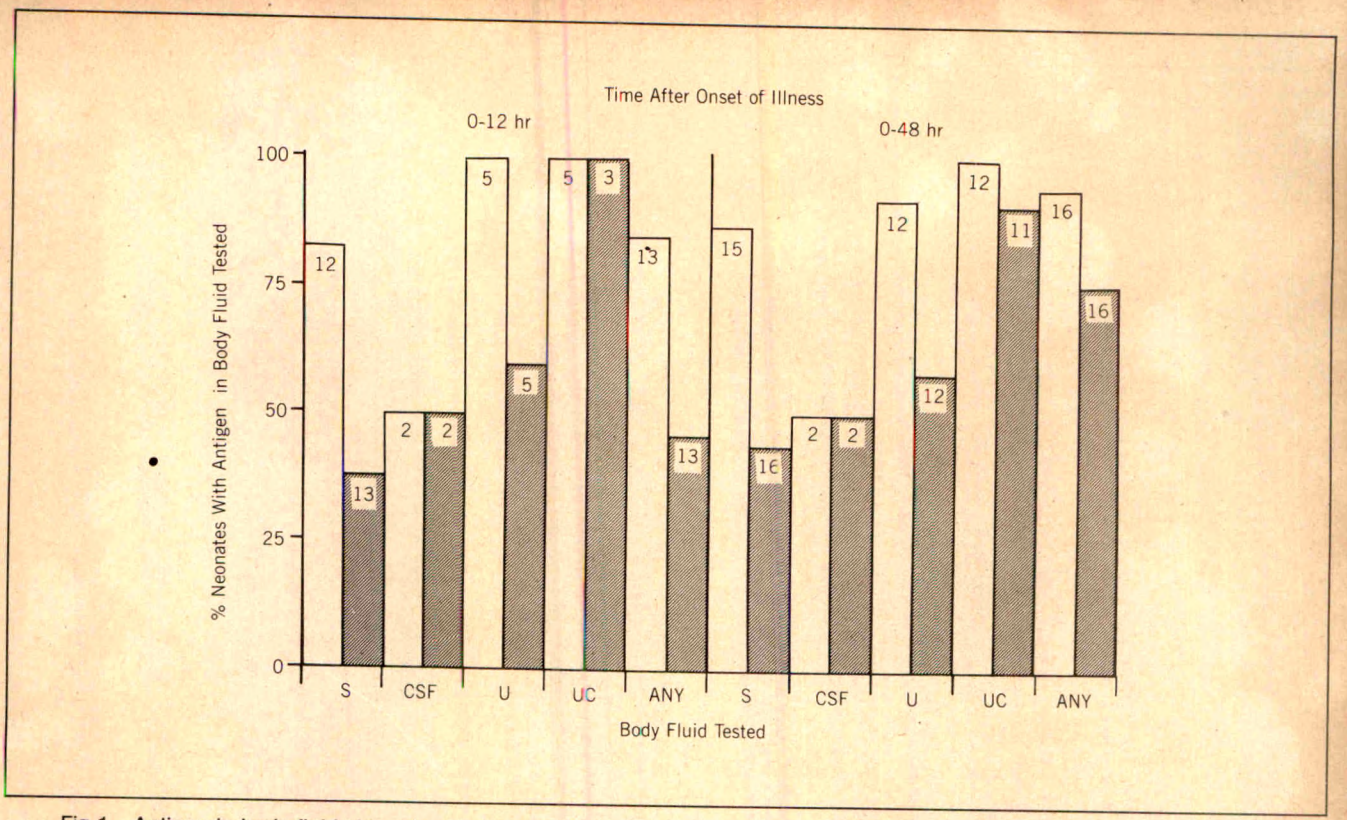
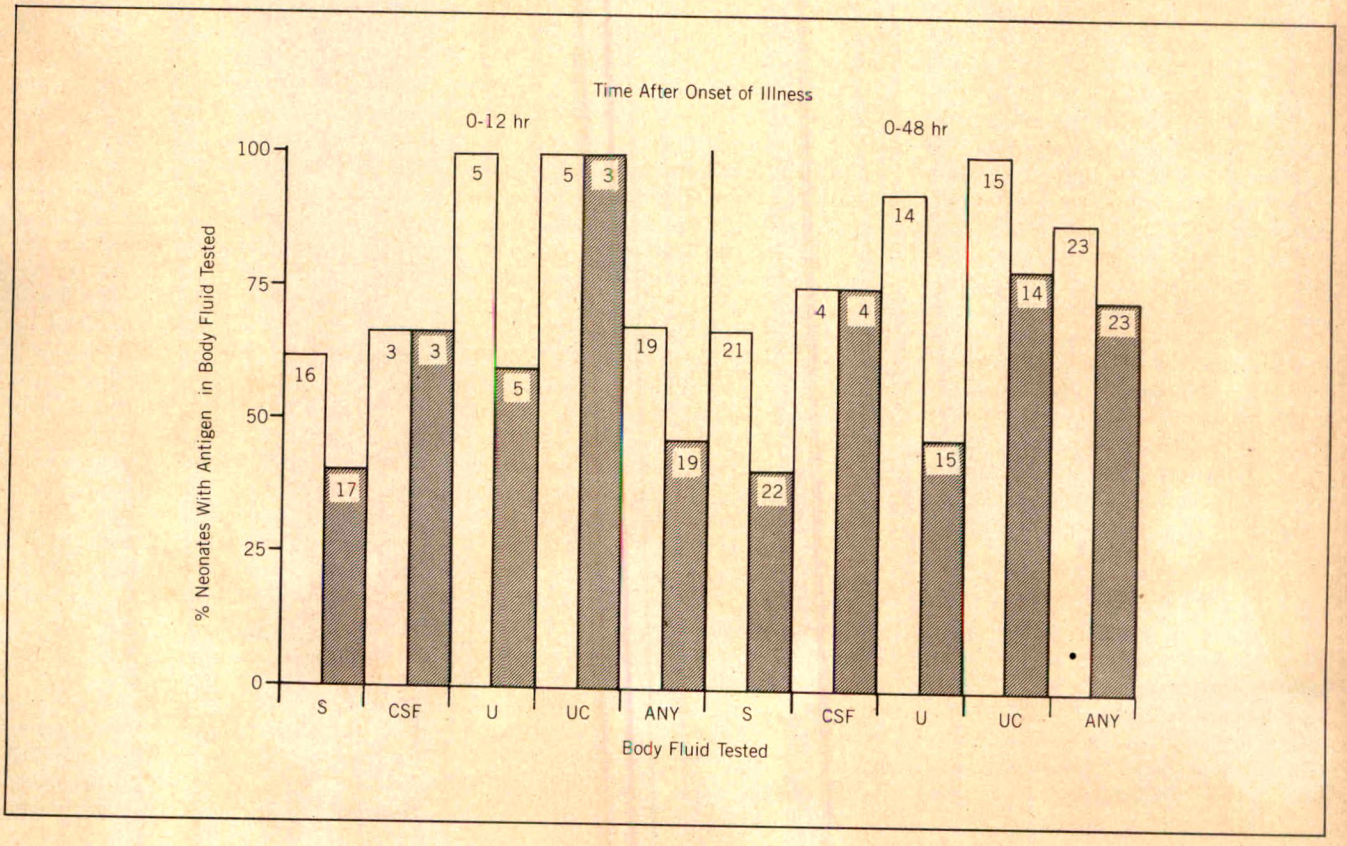


Fig 1.—Antigen in body fluids in early-onset group B streptococcal pneumonia (N = 16): shaded bar indicates positive by countercurrent immunoelectrophoresis; open bar, positive by latex agglutination; S, serum; U, urine; ANY, any fluid tested.

Fig 2.—Antigen in body fluids in all early-onset group B streptococcal disease (N = 23): shaded bar indicates positive by countercurrent immunoelectrophoresis; open bar, positive by latex agglutination; S, serum; U, urine; ANY, any fluid tested.



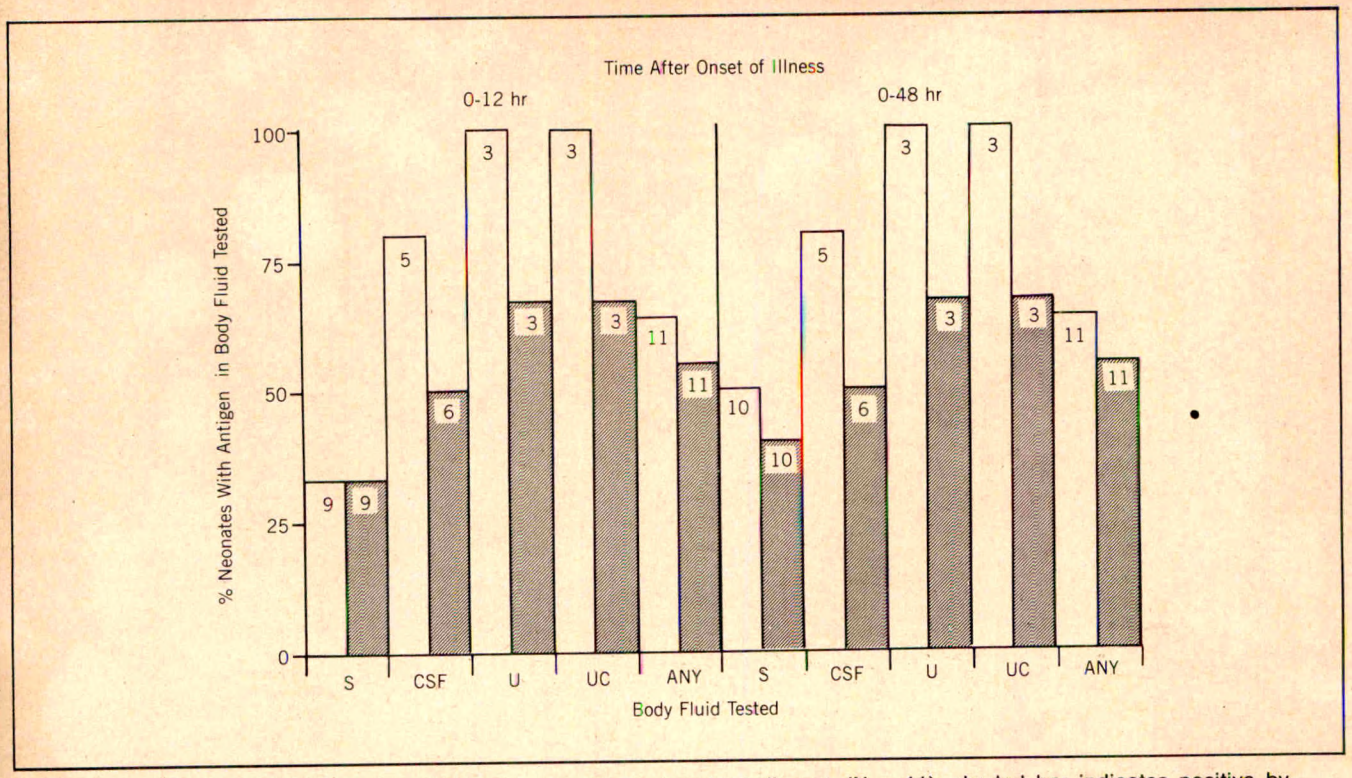


Fig 3.—Antigen in body fluids in late-onset group B streptococcal disease (N = 11): shaded bar indicates positive by countercurrent immunoelectrophoresis; open bar, positive by latex agglutination; S, serum; U, urine; ANY, any fluid tested.

testing (study 1). Three had gastric aspirate Gram's stains and cultures (study 2). Of 12 neonates with late-onset GBS disease, 11 had body fluids available for antigen testing (study 1).

One hundred and nine neonates who were clinically suspected of having an infection and/or RDS in the first 6 hours of life had a gastric aspirate Gram's stain and culture (study 2). These neonates were chosen by those pediatric house officers who routinely include these tests as part of their diagnostic studies in this situation. Other clinically similar neonates cared for by other house officers during the study period were not tested. Study 2 included 16 of 27 neonates with early onset GBS disease, the 11 others did not have gastric aspirate Gram's stains or cultures. Another population group was 100 consecutive neonates with RDS who were included in study 3.

Antigen Detection

All neonates in this study had a positive blood and/or CSF culture. Randomly collected samples of serum, urine, and/or CSF were obtained for testing by both LA and CIE. The time after the onset of clinical illness that they were obtained was noted. Available gastric aspirates that were positive on culture for GBS were tested by CIE. To check for the specificity of finding GBS antigen as an indicator of GBS infection, a negative control group of body fluids was obtained from the following: patients with *Haemophilus influenzae* type b, *Neisseria meningitidis* groups B, C, and Y; patients with *Escherichia coli* or *Streptococcus pneumoniae* meningitis and/or sepsis; neonates who were found not to be infected by culture; and neonates superficially colonized with GBS. Dilutions of 18-hour Trypticase soy broth cultures of GBS types 1a, 1b, 1c, 2, and 3 were used as positive controls. Body fluids, as well as urine concentrated in a disposable ultrafilter system (MINICON B-15) filter (Amicon Corporation, Lexington, Mass) were tested by LA and CIE.

The LA test used was developed by one of us (P.B.) and is a modification of the method of Severin.[10] The latex suspension was prepared by adding 1 part 0.81 μm of latex particles to either 1 part of the γ-globulin fraction of a 1:20 dilution of GBS grouping serum (Atlantic Antibody Co., Westbrook, Me) or whole serum antibody diluted 1:40 using GBS grouping serum (Burroughs Wellcome, Beckenham, England) in glycine-buffered saline (pH, 8.2). After two hours incubation at 37 °C, glycine-buffered saline plus 0.1% bovine serum albumin plus 0.15% sodium azide was added in a 1:1 ratio to the antiserum–latex suspension and stored at 4 °C. For testing, 20 μL of this dilute suspension was added to 40 μL of body fluid on a glass slide, mixed and agitated for three minutes. Agglutination showing at least definite clumps with only a slightly cloudy background was considered positive. Latex particles coated with normal rabbit sera served as a negative control.

Countercurrent immunoelectrophoresis was performed using a power pack (Hyland Austigen II, Hyland Labs, Costa Mesa, Calif) and plates refilled with 16 mL of 1% agarose (Fischer Scientific Co, Pittsburgh) in 0.05M sodium barbital-hydrochloride buffer (pH, 8.0). Three-millimeter wells spaced 5 mm apart were filled with 0.01 mL of body fluid or either GBS grouping serum and underwent electrophoresis at 30 mamp (2.0 V/cm for 1.5 hours). Detection of GBS antigen was attempted in serum, CSF, urine, or concentrated urine after centrifugation using LA and CIE.

Gram-Positive Cocci in Gastric Aspirate

This group included neonates with a maternal history of fever, rupture of membranes of more than 24 hours, foul-smelling amniotic fluid, hyperthermia, hypothermia, apneic spells, hypotension, meconium

aspiration, or tachypnea. Thirty met previously described criteria for RDS.[8-11] Blood cultures, and when indicated, CSF cultures were performed on all neonates. All had a gastric aspirate obtained in the first six hours of life that was Gram's stained and cultured. All with respiratory distress had a chest roentgenogram. A diagnosis of a bacterial infection was made on the basis of a positive blood and/or CSF culture.

Apnea and/or Hypotension

To determine if the finding of nonterminal apnea and/or hypotension was more commonly found in neonates with early-onset GBS pneumonia than RDS, all 19 neonates with early-onset GBS pneumonia and 100 consecutive neonates with RDS were monitored and the findings of nonterminal apneic episodes and/or hypotension in the first 24 hours of life were recorded. Early-onset GBS pneumonia was defined as an illness in neonates less than 8 days old with respiratory distress, a chest roentgenogram positive for infiltrates or having a "ground glass" appearance, and a blood and/or CSF culture containing GBS. Respiratory distress syndrome was defined by previously described clinical and laboratory criteria[8,11] and as having a sterile blood culture. Continuous monitoring was performed for nonterminal apneic spells, defined as being greater than 20 s in duration. Hypotension was defined as a blood pressure of less than or equal to 40 mm Hg by the Doppler technique and checked for at least hourly.

RESULTS

Antigen Detection

A population of 34 neonates with GBS infection was tested. Sixteen had early-onset GBS pneumonia (including two with meningitis), seven had early-onset meningitis and/or sepsis, and 11 had late-onset meningitis and/or sepsis. Eighty percent of these neonates had multiple body fluids tested and 95% of the body fluids were of sufficient volume to test both by LA and CIE. The results were divided into the clinical categories, early-onset pneumonia, all early-onset disease, and late-onset disease and subdivided into antigen detected in body fluids obtained 0 to 12 hours after onset of illness or overall in the first 48 hours after onset of illness (Fig 1 to 3). Since all neonates did not have the same samples collected, the results could not be compared statistically but could be discussed in general terms.

Overall, LA appeared more sensitive than CIE in detecting antigen in body fluids. Latex agglutination detected antigen in 100% of 18 neonates with urine available for concentration. In all disease categories using LA or CIE, concentrated urine was the best body fluid to use to detect antigen. This was followed by urine, then CSF in patients with meningitis and then sera. The percent of body fluids containing GBS antigen was essentially the same in the first 12 hours of illness as in the first 48 hours of illness.

Only eight gastric aspirates (from GBS pneumonia patients) containing GBS by culture were available for antigen testing. Three contained antigen detectable by CIE. Latex agglutination could not be used on gastric aspirates due to their viscosity. Increased in vitro sensitivity of LA over CIE was demonstrated using broth cultures of GBS types 1a, 1b, 1c, 2, and 3. Using the Atlantic or the Burroughs Wellcome GBS antibody, GBS antigen could be detected in the broths to a 1:4 dilution by CIE and to at least a 1:256 dilution by LA. These two antibody preparations gave similar results in the LA and CIE test. The specificity of the two tests was demonstrated in that no GBS antigen was detected in 49 patients infected with bacteria other than GBS, 40 not infected with bacteria, and four only colonized with GBS.

Gram-Positive Cocci in Gastric Aspirate

Of the 109 neonates with respiratory distress or suspected infection tested, 29 neonates had Gram-positive cocci in their gastric aspirates. Their gastric aspirate cultures showed that 17 were GBS, seven α-hemolytic streptococci (*Str pneumoniae*, *Str viridans*, enterococcus or group D *Streptococcus*), one *Staphylococcus epidermidis*, one *Sta aureus*, and three sterile aerobically. Of these 29 neonates, ten had or developed early onset GBS pneumonia and bacteremia, one had GBS meningitis, two had GBS bacteremia, and 1 had *Sta aureus* sepsis. In all cases, the organism from the blood or CSF was the same as that grown from the gastric aspirate. Three neonates in whom RDS developed had α-hemolytic streptococci in their gastric aspirates.

Eighty neonates had no Gram-positive cocci found in their gastric aspirate Gram's stain. Of this group, three gastric aspirate cultures were positive, all GBS. Of these three, GBS pneumonia and bacteremia developed in two and GBS pneumonia and meningitis developed in one. Respiratory distress syndrome developed in 27 neonates who had negative gastric aspirate Gram's stains.

Overall, in 109 neonates with suspected infection or RDS, systemic infectious diseases developed in 14 of 29 (48%) neonates with Gram-positive cocci in their gastric aspirates with these organisms. Early onset GBS disease developed in 13 of the 29 neonates with Gram-positive cocci, ten with early onset pneumonia. Ten of 13 neonates (77%) with early onset GBS pneumonia had Gram-positive cocci in their gastric aspirates, whereas only three of 30 neonates (10%) with RDS had Gram-positive cocci. This difference is highly significant ($P \leq .001$). The clinical significance of culturing GBS from the gastric aspirate in this high-risk group of 109 neonates is demonstrated in that systemic GBS infection developed in 16 of 20 (80%) with GBS in the gastric aspirate.

Apnea and/or Hypotension

Apnea and/or hypotension in the first 24 hours of life were noted in 16 of 19 (84%) of the cases with early onset GBS pneumonia and in 64 of 100 (64%) with RDS. The findings were examined for statistical significance by the χ^2 test. These results were not significantly different ($P > .05$).

COMMENT

Our study demonstrated the usefulness of LA to detect GBS antigen early in the course of early-onset pneumonia, meningitis, and other early- and late-onset GBS infections caused by all types of GBS. Antigen was demonstrated in many samples of sera, CSF, and urine and in all samples of concentrated urine from GBS infected patients. Latex agglutination is rapid, taking three minutes to perform, and is simple to perform.

Edwards et al[7] have previously reported detecting GBS antigen in CSF from patients with GBS type 3 meningitis using LA.

Using CIE, our results confirmed those of Shackelford and Stechenberg[4] who noted that 71% of the cases overall had detectable antigen by 48 hours of illness; 42% had antigen in serum, 70% with meningitis had antigen in CSF, and 93% had antigen in concentrated urine. Siegel and McCracken[5] have noted antigen in body fluids of 14 of 16 (84%) of neonates with GBS meningitis and in three of four (75%) with neonatal bacteremia at the time of diagnosis of the illness vs eight of 13 (61%) and one of three (33%) in our study. These differences may be due to the CIE methodology used, the use of grouping antibody that is less sensitive than type-specific antibody, the patient population studied, or the samples available for testing. In a study of seven neonates with GBS septicemia, Edwards and Baker[6] detected antigen by CIE in the serum of three, urine of three, and concentrated urine of six also emphasizes the value of concentrating urine.

In both our study and that of Edwards et al,[7] LA was more sensitive than CIE. No false-positive results were noted by CIE or LA. As GBS type 3 and *Str pneumoniae* type 14 share a similar capsular polysaccharide, a cross reaction might be noted by these tests.[13] Edwards et al noted one such cross reaction in CSF of a patient with *Str pneumoniae* meningitis type unknown. When using LA, samples must be centrifuged to remove particulate matter that may cause false-positive reactions.

Ablow et al[8] noted four of four cases of GBS pneumonia and zero of one with pure RDS had Gram-positive cocci in the gastric aspirate. Boyle et al[3] noted a positive gastric aspirate Gram's stain in three of three neonates with GBS pneumonia. Our studies confirm that this is a useful test, with 77% of the neonates with early-onset GBS pneumonia and only 10% of the patients with RDS having Gram-positive cocci in their gastric aspirates. Also, in the newborn patients clinically suspected of being infected, there was a 12-fold increased risk of those with Gram-positive cocci in their gastric aspirate developing severe early-onset GBS disease over those without cocci. A similar high risk has been noted if Gram-positive cocci are seen in a tracheal aspirate.[12] There were no cases of *Str pneumoniae* disease. *Streptococcus pneumoniae* could be confused clinically and on Gram's stain with GBS disease as was the *Sta aureus* case in this study.

Ablow et al[8] also noted that apneic spells and/or subjective feelings of shock consisting of mottling, peripheral pallor, and weak pulses were more compatible with GBS pneumonia (seven of eight) than RDS (zero of nine). In our study testing a larger number of patients, apnea and/or hypotension was commonly found in both early-onset pneumonia (84%) and RDS (64%) making this characteristic of little use in distinguishing between these illnesses. A similar finding was reported by Menke et al.[9]

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References

1. Feigin RD: The perinatal group B streptococcal problem: More questions than answers. *N Engl J Med* 294:106-107, 1976.

2. Cochran WD: Hyaline-membrane disease and infection in the newborn. *N Engl J Med* 294:844, 1976.

3. Boyle RJ, Chandler BD, Stonestreet BS, et al: Early identification of sepsis in infants with respiratory distress. *Pediatrics* 62:744-750, 1978.

4. Shackelford PG, Stechenberg BW: Countercurrent immunoelectrophoresis (CIE) in group B streptococcal disease. *Pediatr Res* 11:505, 1977.

5. Siegel JD, McCracken GH: Detection of group B streptococcal antigens in body fluids of neonates. *J Pediatr* 93:491-492, 1978.

6. Edwards MS, Baker CJ: Prospective diagnosis of early-onset group B streptococcal infection by countercurrent immunoelectrophoresis. *J Pediatr* 94:286-288, 1979.

7. Edwards MS, Kasper DL, Baker CJ: Rapid diagnosis of type III group B streptococcal meningitis by latex particle agglutination. *J Pediatr* 95:202-205, 1979.

8. Ablow RC, Driscoll SG, Effmann EL, et al: A comparison of early-onset group B streptococcal neonatal infection and the respiratory-distress syndrome of the newborn. *N Engl J Med* 294:65-70, 1976.

9. Menke JA, Giacoia GP, Jockin H: Group B beta hemolytic streptococcal sepsis and the idiopathic respiratory distress syndrome: A comparison. *J Pediatr* 94:467-471, 1979.

10. Severin WPJ: Latex agglutination in the diagnosis of meningococcal meningitis. *J Clin Pathol* 25:1079-1082, 1972.

11. Thullen JD: Respiratory distress syndrome (RDS) in a district referral center. *NC Med J* 38:645-648, 1977.

12. Sherman M, Goetzman B, Ahlfors C, et al: Tracheal aspiration and its clinical correlates in the early diagnosis of congenital pneumonia. *Pediatr Res* 12:499, 1978.

13. Fischer GW, Lowell GH, Crumrine MH, et al: Immunoprecipitation and opsonic cross-reaction between type-14 pneumococcus and group-B streptococcus type III. *Lancet* 1:75-77, 1979.

Myocardial Infarction in the Neonate With Normal Heart and Coronary Arteries

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• Myocardial infarction is rarely recognized in the newborn. We report two cases in which the infant had a normal heart with normal coronary arteries. A review of previously described cases suggests that the most frequent cause of neonatal myocardial infarction is coronary artery occlusion secondary to paradoxical thromboembolization. It is speculated that infarction also can result from coronary hypoperfusion in asphyxiated infants. This report serves to remind the clinician that myocardial infarction can occur in the neonatal period and that an ECG should be obtained when evaluating a newborn with acute onset of shock.

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Myocardial infarction in the newborn is extremely uncommon. We report two new cases and review the previously reported cases[1-13] in an effort to better define the clinical spectrum and causes of neonatal myocardial infarction.

REPORT OF CASES

CASE 1.—A 2,960-g female infant was born after an uncomplicated 42-week gestation and a normal vaginal vertex delivery. Apgar scores were 9 and 10 at one and five minutes, respectively. The nursery stay and subsequent course at home were uneventful until the morning of admission on the 13th day of life, when the baby cried out, "as if in pain" and became acutely cool and pale. The infant was moribund and ashen. Her pulse rate was 170 beats per minute with a regular rhythm; respirations were 60/min, shallow, and gasping. Peripheral pulses were not palpable and blood pressure was unobtainable. There was no heart murmur or hepatosplenomegaly. The infant was obtunded with absent deep tendon reflexes and only minimal response to pinprick. Arterial blood measurements: fractional concentration of oxygen in inspired gas [FIo_2] 1.00: pH, 6.96; $Paco_2$, 45 mm Hg; Pao_2, 57 mm Hg. The initial chest roentgenogram showed a normal heart size with diminished pulmonary markings. Cardiomegaly and increased pulmonary markings were present on the follow-up chest roentgenogram three days later. The CSF, blood, and urine bacterial cultures and nasopharyngeal and stool viral cultures yielded no growth. An ECG five hours after the onset of pallor was interpreted as consistent with an acute inferolateral myocardial infarction (Fig 1). The creatinine phosphokinase (CPK) and lactic dehydrogenase (LDH) levels 24 hours after the initial presentation were 937 IU/L and 8,700 IU/L, respectively (normal, 5 to 30 IU/L and 40 to 120 IU/L, respectively), and both returned to normal values at the end of one week. Left ventricular dilation and poor left ventricular function was evident on echocardiogram.

The infant was intubated. Intermittent mandatory ventilation was instituted. Persistent hypotension and peripheral vasoconstriction were treated with supplemental fluids, dopamine, and isoproterenol. Sodim bicarbonate and tromethamine were used to correct the metabolic acidosis, and digitalis was begun. The subsequent hospital course was complicated by right-to-left shunting through a patent ductus arteriosus, which resolved with improvement in left ventricular function and increased systemic blood pressure. The baby had seizures on the second hospital day, presumed secondary to cerebral edema and hypoxemia. Cardiac catheterization was performed two weeks after initial examination and demonstrated normal coronary arteries without evidence of occlusion. The left ventricular function was diminished, and there was a dyskinetic lateral segment. One month after hospitalization, the baby appeared normal without evidence of congestive heart failure. The ECG findings showed improvement (Fig 2). Diminished left ventricular function remained evident on echocardiogram.

CASE 2.—A 3,440-g, term, appropriate for gestational age female infant was born by elective cesarean section (indication: previous cesarean section. Apgar scores were 4 and 1 at one and five minutes, respectively. The infant was intubated and given a plasma expander for hypotension. The initial arterial blood measurements were (FIo_2, 1.00): pH, 6.92; Pao_2, 33 mm Hg; $Paco_2$, 77 mm Hg. On admission, the temperature was 37.5 °C, pulse rate was 150 beats per minute, and respirations were 65/min. The blood pressure was 100/40 mm Hg, although the infant did not appear well perfused. She was obtunded and responded only to painful stimuli.

A chest roentgenogram showed a large cardiothymic shadow and possible pulmonary vascular congestion. An ECG at 6 hours of age was interpreted as consistent with an inferolateral myocardial infarction (Fig 3). Diminished left ventricular function was evident on echocardiogram.

Despite therapy, the patient had persistent hypoxemia and a combined respiratory and metabolic acidosis. A 30-mm Hg difference in Pao_2 between right radial and umbilical artery catheter blood gas levels was noted. Administration of tolazoline, epinephrine, and isoproterenol resulted in no clinical response. The infant died at 29 hours of age.

At autopsy, the heart weighed 22.8 g. Grossly, the free wall of the left ventricle was soft to palpation and had a dark red discoloration consistent with an acute myocardial infarction. The foramen ovale was probe-patent and the ductus arteriosus was widely patent. The coronary arteries were anatomically normal, and all branches were patent without evidence of thrombi. The umbilical vein and ductus venosus were free of thrombi. The lungs appeared consolidated. The rest of the gross examination findings were within normal limits.

Microscopic examination of the sections of the left ventricle revealed massive

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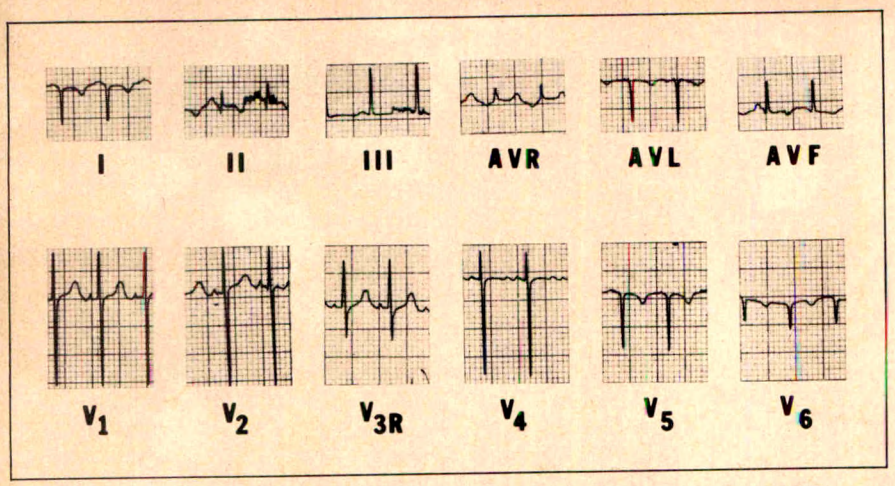

Fig 1.—Initial ECG in patient 1 at 13 days of age, showing Q waves in I, V_{5-6} and T-wave inversion in I, II, aV_L, aV_F, V_{5-6}, consistent with inferolateral myocardial infarction.

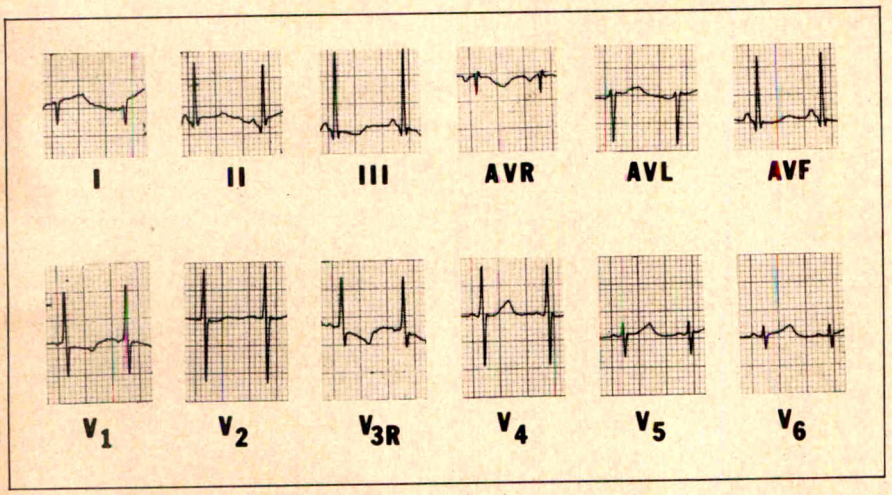

Fig 2.—Electrocardiogram of patient 1 at 2 months of age demonstrates resolution of Q waves and T-wave inversions.

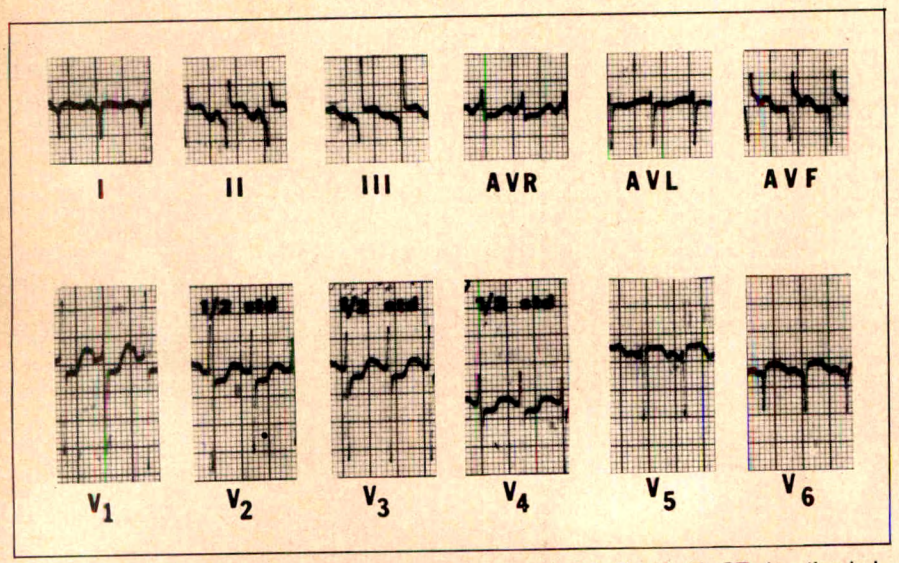

Fig 3.—Case 2; ECG at 6 hours of age shows Q waves in I, II, III, aV_F, V_6, ST elevation in I, aV_L, consistent with inferolateral myocardial infarction.

hemorrhage and necrosis. Serial sections of the coronary arteries were examined and revealed no intimal changes or thrombi.

COMMENT

Although myocardial infarction in the newborn is rarely recognized, two cases are reported herein in which the diagnosis was made early in the clinical course. Each infant manifested peripheral cardiovascular collapse and a persistent metabolic acidosis. The ECG in both cases had Q waves and T-wave inversions consistent with myocardial injury. In case 2, the diagnosis of myocardial infarction was confirmed by postmortem findings. Patient 1 survived and, therefore, there was no tissue examination. Although similar ECG and enzyme changes may be seen in myocarditis, and although this possibility cannot be completely ruled out, the failure to isolate an infectious agent and the clinical findings favor the diagnosis of myocardial infarction in our patient. Extreme elevations of CPK and LDH levels suggest that, in addition to myocardial necrosis, widespread tissue injury occurred, most likely secondary to the marked hypoxemia and hypotension.

Myocardial infarction in the newborn is usually seen in association with congenital heart disease, specifically, obstructive lesions (ie, aortic stenosis),[14,15] anomalous origin of the left coronary artery,[16] and tricuspid atresia.[17] It also has been described in association with hematologic abnormalities.[18,19] Myocardial infarction in older infants has been recognized secondary to degenerative and inflammatory disease of the coronary arteries.[15] In the absence of an underlying systemic disorder or anatomical abnormality, neonatal myocardial infarction is unusual, and, to our knowledge, only 13 previous cases have been reported.[1-13] The condition was diagnosed in eight ante mortem.[4-9,11-12]

The clinical manifestations of our two patients are similar to those previously reported.[1-13] As demonstrated by these 15 cases, neonatal myocardial infarction must be considered in a newborn who has an acute onset of shock and a severe metabolic acidosis. Neonatal myocardial infarction may be complicated by right-to-left shunt-

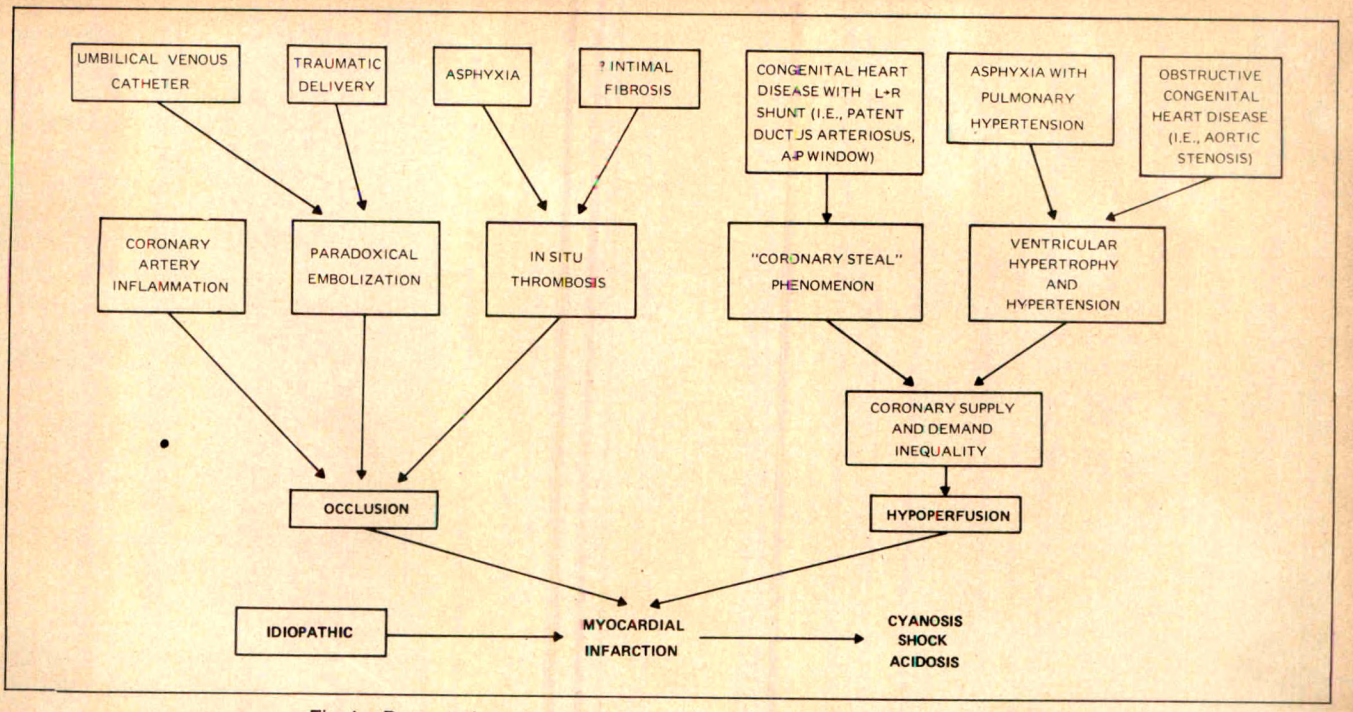

Fig 4.—Proposed mechanisms leading to neonatal myocardial infarction.

ing through a patent ductus arteriosus, a situation that may initially mimic persistent pulmonary hypertension of the newborn. Recognition of the correct diagnosis is imperative prior to therapeutic intervention, as use of tolazaline in an infant with ventricular dysfunction may accentuate systemic hypotension and increase right-to-left shunting.

Although there are several diagnostic considerations that the clinician must exclude when presented with a newborn in shock, an ECG can accurately diagnose myocardial injury if it is present. Of the reported cases of myocardial infarction, 12 had an ECG obtained as part of their evaluation. The initial ECG abnormalities were specified in 11, and of these, nine demonstrated Q waves and ST-T wave changes in the anterior, inferior, and lateral leads. Contrary to the usual initial ECG findings of ST elevation in adults with myocardial infarction,[20] only two infants had ST segment changes alone on their ECGs.[6,9]

The ECG changes may be initially misinterpreted. Deep Q waves in the lateral precordial leads with diminished or absent left-sided forces may suggest the hypoplastic left heart syndrome, but this diagnosis may be ruled out by echocardiogram.[13] A myocardial injury pattern on the ECG may also be initially misinterpreted as type B Wolff-Parkinson White syndrome.[10] However, Q waves and ST-T wave changes in conjunction with the clinical setting of shock and acidosis in the newborn should make the clinician suspect a myocardial infarction.

There are several possible causes of myocardial infarction in the newborn. Coronary thrombosis has been reported twice.[4,13] Gault and Usher[4] described an infant with coronary artery thrombosis associated with focal intimal thickening. They stated that although thrombosis is unusual, intimal changes are frequent findings in newborns without heart disease. Moon[21] has suggested that intimal proliferation may reflect tissue reaction to a perinatal asphyxial insult, and he reported that the histologic changes were identical to those seen in the early phases of arteriosclerosis in adults. These intimal changes have not been noted in other reported cases of neonatal myocardial infarction.

The most frequent cause of neonatal myocardial infarction appears to be embolic injury. One infant had an air embolism apparently secondary to placement of an umbilical venous catheter.[11] Postmortem examinations in six other cases demonstrated a coronary artery thromboembolus,[1,6-9,12] and in four of these, thrombus formation was found in the ductus venosus or in the umbilical vein.[7-9,12] All had a widely patent foramen ovale and/or ductus arteriosus. These findings suggest that infarction occurred secondary to paradoxical thromboembolization, with the thrombus originating in the umbilical venous system. In two cases, the embolization was temporally related to the placement of an umbilical venous catheter. Thrombus formation is commonly associated with such catheters,[22] and was the probable source of the thromboemboli in these two cases. Presumably, in the other four cases, thrombus formed in the ductus venosus or umbilical vein secondary to cord compression or stasis following birth asphyxia. This hypothesis is supported by the fact that the most frequent predisposing factor in all the cases reviewed appeared to be a difficult delivery, often associated with a breech extraction or cord prolapse.

Three of the cases of neonatal myocardial infarction,[2,3,10] in addition to our case 2, had no postmortem evidence of thrombosis or thromboembolization. Therefore, the pathogenesis of infarction in these infants is unclear. It is possible that they could have suffered a coronary occlusion that was not evident at examination because of thrombolysis or clot retrac-

tion. However, since each infant died within hours of infarction (range, nine to 29 hours), one would expect some residual evidence of the thrombus or intimal reactive changes. We believe it is more likely that these infants suffered myocardial injury secondary to impaired coronary artery perfusion. The common denominator for all four of these infants was neonatal asphyxia. Myocardial ischemia, secondary to coronary hypoperfusion, has been described in hypoxic term infants.[23] Rowe and Hoffman[23] have proposed that these infants may have an excessively brisk pulmonary vasoconstrictive response to hypoxia, leading to right ventricular hypertrophy and excessive demands on the coronary arterial supply. Subendocardial ischemia also has been seen in a group of infants who had respiratory distress and a patent ductus arteriosus.[24] It is suggested that the cause of the diminished coronary perfusion in these infants is a "ductal steal" phenomenon.[24] In addition to these examples of myocardial ischemia, there is evidence from postmortem examination of infants dying with congenital heart disease that circulatory disturbances of the coronary arteries can lead to myocardial infarction.[14,17]

While diminished coronary perfusion probably occurs frequently in asphyxiated newborns, transmural infarction would appear to be an unusual consequence.[25] When it does occur, it probably results from a combination of factors, ie, hypoxemia, excessive pulmonary vasoconstriction with ventricular hypertension and increased cardiac work, and perhaps diminished perfusion from a "ductal runoff." A patient in whom the right coronary artery supplies a large portion of the posterior wall of the left ventricle may have an increased susceptibility to several of these factors.[23]

In addition to these mechanisms, coronary spasm, which has been reported as a cause of myocardial ischemia and occasionally infarction in adults,[26,27] also might be suggested as a factor leading to myocardial damage in the newborn. However, myocardial infarction following coronary spasm in adults usually has been reported in patients with severely narrowed coronary arteries.[28] Therefore, it would seem unlikely that coronary spasm by itself would be a significant etiologic factor in myocardial infarction in the newborn. However, it has been demonstrated by angiography in adults that coronary spasm can be precipitated by α-adrenergic agonists.[29] In a stressed newborn with a marked catecholamine response, coronary spasm may, in some cases, accentuate a myocardial hypoperfusion state.

The two pathways for infarction appear to be (1) coronary artery occlusion, and (2) diminished coronary perfusion without occlusion (Fig 4). Case 1 cannot be readily explained by either of the proposed mechanisms. As a result, the cause of the infarction in this case remains unknown.

These case reports serve to remind the clinician that myocardial infarction can occur in an otherwise healthy newborn. An ECG should be obtained when an infant has an acute onset of shock, especially if there is a delivery history consistent with cord compression or asphyxia, or a history of an umbilical venous catheterization.

Frederick Parkhurst, MD, and Harry Laws, MD, referred these cases, and Jan Gerhardy and Cheryl Noles provided secretarial assistance.

Nonproprietary Name and Trademark of Drug

Isoproterenol—*Norisodrine.*

References

1. Stryker WA: Coronary occlusive disease in infants and children. *Am J Dis Child* 71:280-300, 1946.
2. Ravich RM, Rosenblatt P: Myocardial infarction in the newborn infant. *J Pediatr* 31:266-273, 1947.
3. Richart R, Benirschke K: Myocardial infarction in the perinatal period. *J Pediatr* 55:706-712, 1959.
4. Gault MH, Usher R: Coronary thrombosis with myocardial infarction in a newborn infant. *N Engl J Med* 263:379-382, 1960.
5. Fagan LF, Thurmann N, LoPiccolo VF Jr, et al: Myocardial infarction in the perinatal period with long-term survival. *J Pediatr* 69:378-382, 1966.
6. Hauwaert Van der LG, Loos MC, Verhaeghe LK: Myocardial infarction during exchange transfusion in a newborn infant. *J Pediatr* 70:745-750, 1967.
7. Arthur A, Cottom D, Evans R, et al: Myocardial infarction in a newborn infant. *J Pediatr* 73:110-114, 1968.
8. Berry CL: Myocardial infarction in a neonate. *Br Heart J* 32:412-415, 1970.
9. Guller B, Bozic C: Right-to-left shunting through a patent ductus arteriosus in a newborn with myocardial infarction. *Cardiology* 57:348-357, 1972.
10. Iannone LA, Duritz G, McCarty RJ: Myocardial infarction in the newborn: A case report complicated by cardiogenic shock and associated with normal coronary arteries. *Am Heart J* 89:232-235, 1975.
11. Grubbauer HM, Schutt B, Gertsch M, et al: Herzinfarkt nach Embolie bei einem Neugeborenen. *Helv Paediat Acta* 31:53-59, 1976.
12. Fletcher MA, Meyer M, Kirkpatrick SE, et al: Myocardial infarction associated with umbilical cord hematoma. *J Pediatr* 89:806-807, 1976.
13. Sapire DW, Markowitz R, Valdes-Dapena M, et al: Thrombosis of the left coronary artery in a newborn infant. *J Pediatr* 90:957-959, 1977.
14. Franciosi RA, Blanc WA: Myocardial infarction in infants and children: I. A necropsy study in congenital heart disease. *J Pediatr* 73:309-319, 1968.
15. Bor I: Myocardial infarction and ischemic heart disease in infants and children. *Arch Dis Child* 44:268-281, 1969.
16. Askenazi J, Nadas AS: Anomalous left coronary artery originating from the pulmonary artery: Report on 15 cases. *Circulation* 51:976-987, 1975.
17. Hanes TE, Page DL, Graham TB, et al: Regional myocardial infarction of low-flow type in a neonate with tricuspid atresia. *Arch Pathol Lab Med* 101:86-88, 1977.
18. Gadoth N, Kornmehl P, Gueron M, et al: Hemorrhagic infarction of the myocardium in a newborn with haemoglobin H disease and erythroblastosis. *Acta Paediatr Scand* 67:245-247, 1978.
19. Favara BE, Franciosi RA, Butterfield LJ: Disseminated intravascular and cardiac thrombosis of the neonate. *Am J Dis Child* 127:197-204, 1974.
20. Marriott HJL: *Practical Electrocardiography.* Baltimore, Williams & Wilkins Co, 1972, pp 238-247.
21. Moon HD: Coronary arteries in fetuses, infants and juveniles. *Circulation* 16:263-267, 1957.
22. Kitterman JA, Phibbs RH, Tooley WH: Catheterization of umbilical vessels in newborn infants. *Pediatr Clin North Am* 17:895-912, 1970.
23. Rowe RD, Hoffman T: Transient myocardial ischemia of the newborn infant: A form of severe cardiorespiratory distress in full-term infants. *J Pediatr* 81:243-250, 1972.
24. Way GL, Pierce JR, Wolfe RR, et al: ST depression suggesting ischemia in neonates with respiratory distress syndrome and patent ductus arteriosus. *J Pediatr* 95:609-610, 1979.
25. Rowe RD, Izukawa T, Mulholland HC, et al: Nonstructural heart disease in the newborn. *Arch Dis Child* 53:726-730, 1978.
26. Johnson AD, Detwiler JH: Coronary spasm, variant angina and recurrent myocardial infarction. *Circulation* 55:947-950, 1977.
27. Athanassopoulos CB, Maroutsos CG: Prinzmetal's angina. *Br Heart J* 39:911-913, 1977.
28. Arnett EN, Roberts WC: Acute myocardial infarction and angiocardiographically normal coronary arteries, an unproven combination. *Circulation* 53:395-399, 1976.
29. Yasue H, Touyama M, Kato H, et al: Prinzmetal's variant form of angina as a manifestation of α-adrenergic receptor-mediated coronary artery spasm: Documentation by coronary arteriography. *Am Heart J* 91:148-155, 1977.

The Epidemiology of Poisoning From Drug Products

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• On the basis of 24,487 telephone calls to a poison control center during a one-year period, the 12 most commonly ingested drugs (accounting for 2,417 calls) were selected for study. Each agent was analyzed on the basis of (1) age of the individuals involved, (2) frequency of overdose, and (3) signs, and symptoms, and severity. These findings have implications for the diagnosis and prevention of drug overdose.

(*Am J Dis Child* 134:763-765, 1980)

An awareness of the epidemiology of potentially poisonous substances is useful for the clinician in dealing with acute overdoses.[1-5] By focusing on what is commonly encountered in the clinical setting, greater accuracy in diagnosis and a more rational approach to prevention are possible.

METHODS

In an effort to determine the characteristics of poisoning from prescription and nonprescription medications, information on all telephone calls to a poison control center relating to drug ingestion between July 1977 and June 1978 were analyzed.[6] The information was recorded by poison information specialists, then coded, keypunched, and entered in a computer.

Of 24,487 drug and household product overdoses over the one-year period, the 12 most commonly ingested drugs (representing 2,417 calls) were analyzed in detail. Drug products were defined as chemical compounds available to the public and intended for specific therapeutic effect. Overdoses occurred by the oral, cutaneous, or pulmonary routes. Four age groups were considered for analysis: group 1, 0 to 5 years of age; group 2, 6 to 12 years; group 3, 13 to 20 years; group 4, older than 20 years. Signs and symptoms reviewed included nausea, vomiting, lethargy, dizziness, coughing, choking, dyspnea, ataxia, coma, convulsions, cyanosis, and hypotension. An estimation of severity was determined by the ratio of signs and symptoms to exposures.

RESULTS

Of the 1,975 overdoses in which age of the subject was known, 60% were in group 1, 4% in group 2, 9% in group 3, and 27% in group 4. The frequency of overdose with each of the 12 most common drugs in each age group is presented in Fig 1. In group 1, aspirin was the most commonly ingested drug, followed by vitamins and acetaminophen; in group 2, aspirin, followed by vitamins, isopropyl alcohol, and acetaminophen; in group 3, aspirin, followed by diazepam, acetaminophen, and phencyclidine hydrochloride; and in group 4, diazepam, followed by flurazepam hydrochloride and acetaminophen.

Signs and symptoms occurred in 21% of the overdoses—23% in group 1, 4% in group 2, 22% in group 3, and 51% in group 4. The frequency of signs and symptoms for each of the 12 drug products is presented in Fig 2. In group 1, a combination of brompheniramine maleate, phenylephrine hydrochloride, and phenylpropranolamine hydrochloride (Dimetapp) and aspirin produced the greatest frequency of signs and symptoms; in groups 2 and 3, diazepam and aspirin; and in group 4, diazepam and flurazepam. When severity of the ingestion was considered, based on a ratio of signs and symptoms to exposure for a given product (Fig 2), phencyclidine ingestion was most serious, followed by ingestion of diazepam, a combination of oxycodone, oxycodone terephthalate, caffeine, aspirin, and phenacetin (Percodan), and flurazepam.

Seventy-four percent of the overdoses were accidental, and 26% were purposeful (suicide attempts and drug abuse). Of 1,463 accidental overdoses, 25% were due to aspirin, 16% to vitamins, 12% to acetaminophen, and 10% to isopropyl alcohol. Of 493 suicide attempts, 43% involved diazepam, 13% flurazepam, 12% aspirin, and 11% ace-

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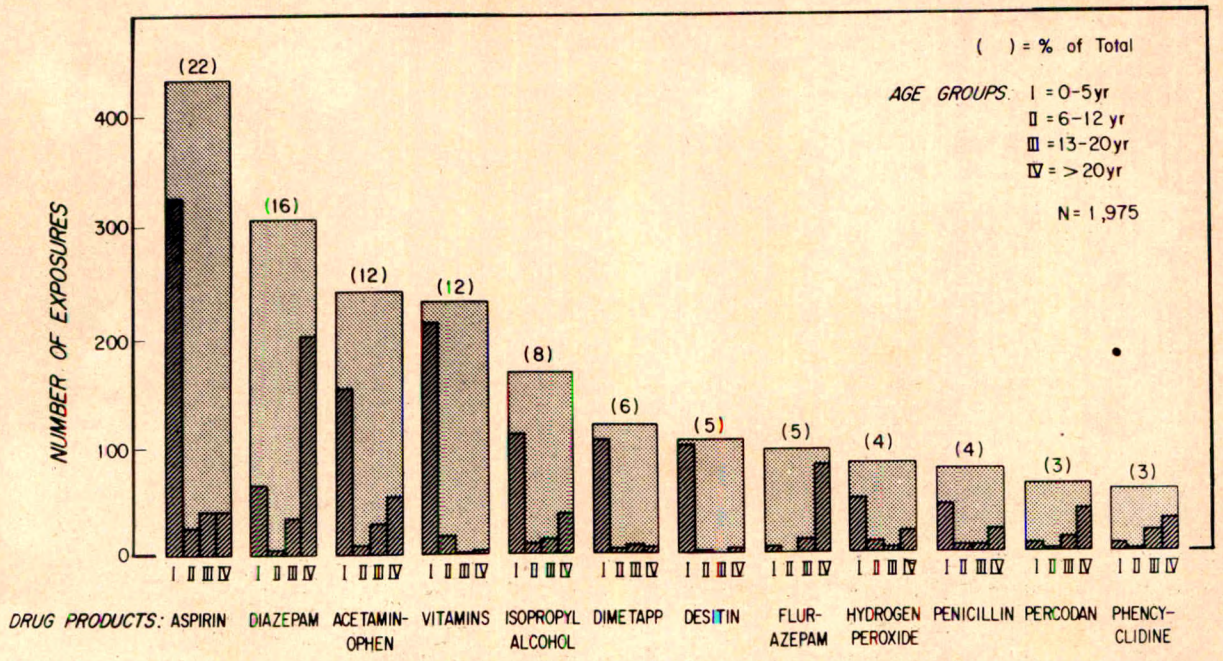

Fig 1.—Descending order of frequency for 12 most common causes of drug overdoses, illustrating number and percentage of exposures for each. Number of exposures in each age group for each drug is illustrated by cross-hatched bars.

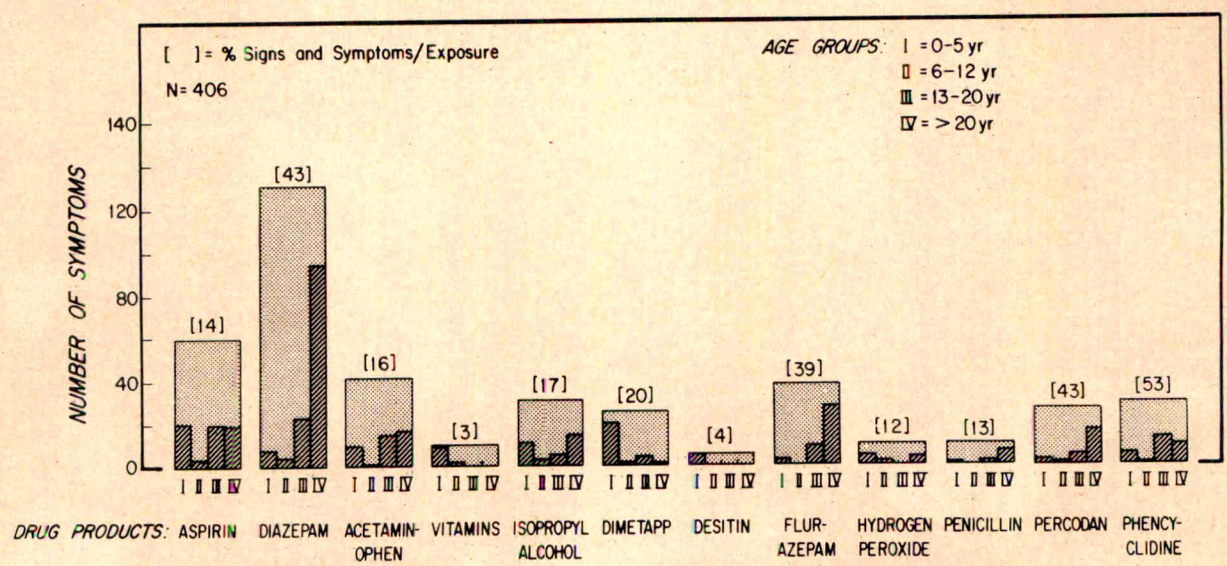

Fig 2.—Frequency of symptoms and relative severity (signs and symptoms per exposures) for 12 most common causes of drug overdoses. Frequency of symptoms in each age group for each drug is illustrated by cross-hatched bars.

taminophen. Phencyclidine was the most commonly abused drug.

COMMENT

This study of the 12 most commonly ingested drugs represented 10% of all calls reported to this poison control center during a one-year period. Children were most likely to ingest drugs for fever (aspirin, acetaminophen), nasal decongestion (Dimetapp), and rash (zinc oxide and cod liver oil combination [Desitin]), as well as vitamins and isopropyl alcohol. Adults were most likely to ingest sedatives (diazepam, flurazepam), analgesic or antipyretic medications (Percodan, aspirin, and acetaminophen), and phencyclidine.

Aspirin and acetaminophen together accounted for 23% of the calls involving suicide attempts (12% and 11%, respectively). In addition, aspirin was the most commonly ingested drug product in groups 1, 2, and 3, while acetaminophen was among those drugs most commonly ingested in all four age groups. Aspirin was the most frequent cause of signs and symptoms in group 1, caused signs and symptoms in equal frequency with diazepam in groups 2 and 3, and was surpassed in frequency only in group 4 by diazepam and flurazepam. These data suggest that continued education—directed not only at children under 5 years of age, but also at the adolescent and adult—is warranted to increase awareness that both aspirin and acetaminophen are associated with substantial risk.

Diazepam and flurazepam were, respectively, the second and eighth most common cause of drug overdose, the first and second most common cause of symptoms, and the second and fourth most severe (signs and symptoms per exposures). Approximately 60% of the suicide attempts involved diazepam and flurazepam. These figures suggest that great care is necessary when prescribing a benzodiazepine to any patient who is prone to self-injury.

Percodan ranked 11th as a cause of drug overdose, fourth as a cause of signs and symptoms, and third in severity. Before prescribing Percodan for analgesia, the risk of overdose or abuse must be carefully considered.

While we found phencyclidine to be the 12th most common cause of drug overdose, it had the second most frequent rate of signs and symptoms and was the most serious as defined by the ratio of signs and symptoms to exposures. The serious nature of phencyclidine toxicity needs to be continually emphasized to the drug-abusing adolescent and young adult.

Vitamins, isopropyl alcohol, Dimetapp, Desitin, hydrogen peroxide, and penicillin are the most common causes of overdose in children aged 5 years and under. Vitamins, Desitin, hydrogen peroxide, and penicillin produced signs and symptoms infrequently when contrasted to the six drugs already discussed. All six drugs remain strong justification for continued poison prevention education focused on the pediatric population.

This study draws attention to the 12 drug products most commonly ingested. It is hoped that these data will serve to increase physician awareness of those drug products of greatest risk and hence lead to improved diagnosis. In addition, consideration of the most common drugs ingested, the age of the patient involved, and the underlying reason for the poisoning are all necessary to carry out effective poison prevention efforts. Finally, the data indicate the need for poison control centers to expand their focus of poison prevention activities to the adolescent and adult, in whom morbidity and mortality are high and the potential gains for new methods of preventing drug abuse and suicide could have considerable impact.

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References

1. Goulding R, Ashforth GK, Jenkins H: Household products and poisoning. *Br Med J* 1:286-287, 1978.

2. Lovejoy FH Jr, Gouveia W, Edlin AI: Childhood poisoning with toilet and cosmetic articles. *Pediatrician* 6:226-231, 1977.

3. Done AK: Poisoning from common household products. *Pediatr Clin North Am* 17:569-581, 1970.

4. Lovejoy FH Jr, Flowers J, McGuigan MA: The epidemiology of poisoning from household products. *Vet Hum Toxicol* 21:33-34, 1979.

5. Lawrence RA, Haggerty RJ: Household agents and their potential toxicity. *Mod Treat* 4:633-647, 1967.

6. Lovejoy FH Jr, Caplan DL, Rowland T, et al: A statewide plan for care of the poisoned patient: The Massachusetts poison control system. *N Engl J Med* 300:363-365, 1979.

Early-onset Sepsis and Pneumonia Observed as Respiratory Distress Syndrome

Assessment of Lung Maturity

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• **Lung maturity was assessed in nine neonates with early-onset sepsis and/or pneumonia first observed as respiratory distress syndrome (RDS). All but one infant had at least one clinical or laboratory feature in the immediate postnatal period that suggested infection. Five patients had a mature phospholipid pattern in tracheal or gastric secretions, suggesting that RDS was not present; four patients had an immature pattern, suggesting that RDS coexisted with early-onset sepsis and/or pneumonia. Neither clinical nor radiologic features differentiated patients whose surfactant phospholipid patterns were mature from those whose patterns were immature. The presence of a mature surfactant complex in an infant with RDS should suggest the presence of infection. The presence of an immature pattern, however, does not exclude the presence of infection since RDS may coexist with early-onset sepsis and/or pneumonia.**

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Recently, it has been recognized that sepsis and pneumonia with group B streptococcus (GBS), *S pneumoniae*, *S bovis*, and *Haemophilus influenzae* may have clinical features similar to respiratory distress syndrome (RDS) of the newborn.[1-5] There have been several brief reports on the status of lung maturity in patients with RDS due to early-onset GBS sepsis.[6-8] All but one of these reports[8] have suggested that patients with GBS sepsis have mature values for pulmonary surfactant, as assessed by the "shake test" on gastric aspirate[7,8] or by the phospholipid composition of tracheal aspirate.[6] The present study reports on the phospholipid composition of the tracheal or gastric aspirates of nine newborn infants with early-onset sepsis and/or pneumonia first observed as RDS and correlates these with clinical and radiological findings.

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PATIENTS AND METHODS

Patient Selection

All patients were hospitalized in the Infant Special Care Center, University of

Case	Birth Weight, g/ Gestational Age, wk
Mature phospholipid pattern	
1	3,280/36
2	3,033/38
3	2,500/35
4	2,325/34
5	1,900/34
Immature phospholipid pattern	
6	1,520/32
7	1,440/32
8	1,100/30
9	900/29

California Medical Center, San Diego, between September 1977 and June 1979. All patients with early onset of sepsis and/or pneumonia (within the first few hours of life) mimicking RDS, both clinically and radiologically, were included in this report. Patients with early onset of sepsis but with a normal chest roentgenogram or one displaying obvious pneumonia (focal infiltrates or consolidation) were excluded because a diagnosis of RDS was not considered. Clinical records were reviewed retrospectively. Chest roentgenograms were read without knowledge of clinical history.

Surfactant Maturity Studies

Gastric aspirates were collected after birth; tracheal aspirates were collected by routine suctioning of each infant during the first 24 hours of life. If the amount of lipid in the tracheal secretions was inadequate, material from several tracheal aspirates obtained in the first 24 hours were combined. Lipid extraction was performed by a modification of the technique by Bligh and Dyer,[9] using chloroform and methanol (2:1, v/v). Phospholipids were separated after cold acetone precipitation (which concentrates the disaturated lecithin) by two-dimensional thin-layer chromatography as described previously.[10] Both acetone-precipitable and acetone-soluble fractions were spotted separately and run in parallel in the first dimension (solvent: chloroform-methanol-water-glacial acetic acid [65:24:4:8, v/v/v/v]). The acetone-precipitable (disaturated) fraction was run in the second dimension perpendicular to the first run after drying at 70 °C for five minutes (solvent: tetrahydrofuran-methyla1-methanol-2*N* ammonium hydroxide [40:28.5:7.8:4.2, v/v/v/v]). This technique separates highly saturated lecithin and other phospholipids, including sphingomyelin, phosphatidylserine, phosphatidylinositol (PI), phosphatidylethanolamine, and phosphatidylglycerol (PG), that are present in the acetone-precipitable fraction; the acetone-soluble fraction principally contains unsaturated lecithin. Individual phospholipids were quantified by reflectance densitometry, expressed as percentage of total phospholipid in the acetone-precipitable fraction. In addition, the lecithin-sphingomyelin (L/S) ratio and the percent of total lecithin precipitated by cold acetone were also calculated as previously described.[11]

RESULTS

Clinical and laboratory data on the nine patients are outlined in the Table. The diagnosis of sepsis and/or pneumonia was made in all but one patient by culturing the appropriate organism from the blood and other sources. A single patient (No. 5), who had been treated with antibiotics prior to obtaining appropriate cultures, had a tracheal aspirate positive for GBS by the technique of counterimmunoelectrophoresis. None of the patients had meningitis. The organisms identified were GBS, *H influenzae*, *S pneumonia*, and *Escherichia coli*. Although only one patient (No. 6) had a prenatal history suggesting infection, all but one infant (patient 1) had at least one clinical or laboratory finding in the immediate postnatal period suggesting its presence. Early onset of shock and leukopenia was frequently correlated with the presence of infection. When done, a Gram's smear of the gastric aspirate showing large numbers of Gram-positive cocci also was helpful in detecting GBS infection. Thrombocytopenia was evident only after the first day of life.

Radiologic features suggesting RDS[12] were present in all cases on the initial roentgenogram obtained within the first few hours of life. These included fine, diffuse granularity (eight cases), air bronchograms (seven cases), and/or symmetrical, homogeneous involvement of both lungs (seven cases). Cardiomegaly, which has been described as a frequent feature of

ical, Laboratory, and Surfactant Phospholipid Data on First Day of Life

Outcome	Rupture of Membranes, hr	Signs of Infection	Organism/Source	Onset of Symptoms	L/S Ratio	Precipitable Lecithin, %	Phosphatidylinositol, %	Phosphatidylglycerol
Survived	0	None	*Streptococcus pneumoniae*/blood	Birth	2.3	68	27	+
Survived	7	Apnea, shock, leukopenia	*Haemophilus influenzae* type A/blood	4 hr	2.4	63	27	–
Died	?	Shock	*Escherichia coli*/blood, lung	Birth	2.7	62	14	+
Survived	1	Shock, leukopenia	GBS*/blood, gastric aspirate	1 hr	2.8	52	26	+
Survived	5	Shock, leukopenia	GBS/tracheal aspirate (CIE*)	Birth	3.5	69	16	+
Survived	41	Maternal leukocytosis, shock, leukopenia, Gram-positive cocci in gastric aspirate	GBS/blood, trachea, gastric aspirate	Birth	1.4	45	12	–
Died	16	Shock, leukopenia, thrombocytopenia	*H influenzae* type B/blood, tracheal aspirate	Birth	1.4	46	1.0	–
Survived	?	Leukopenia, Gram-positive cocci in gastric aspirate	GBS/blood, trachea, gastric aspirate	Birth	2.2	29	13	–
Died	0	Shock, leukopenia,† chorioamnionitis	GBS/blood, lung	Birth	0.6	32	4.0	–

*GBS indicates group B streptococcus; CIE, counterimmunoelectrophoresis; L/S, lecithin-sphingomyelin.
†The WBC count was < 10,000/cu mm.

GBS,[13] was noted in only one patient. Underaeration, which is usually seen in cases of RDS, was noted in only two patients. The most consistent feature suggesting infection[14] was the presence of pleural fluid in areas other than the fissures (apices and costophrenic angles); this was noted in seven cases. All patients demonstrated at least one feature not typical for uncomplicated RDS.

Five patients had a mature surfactant phospholipid pattern, while four patients had an immature pattern usually found in RDS.[15,16] Patients with mature patterns in tracheal aspirates had higher L/S ratios; greater amounts of acetone-precipitable (primarily disaturated) lecithin; and the presence of PG or, if absent (as in patient 2), a relatively large amount of PI.

The presence of PG in amniotic fluid or tracheal aspirates excludes the diagnosis of RDS.[15,17] In the absence of PG, a relatively large amount of PI (>20%) with a high L/S ratio and a large amount of disaturated lecithin also suggest that RDS is absent.[17]

The only clinical features that distinguished patients with a mature tracheal phospholipid pattern from those with an immature pattern were birth weight and degree of maturity; all infants with a mature pattern weighed ≥1,900 g and were of ≥34 weeks' gestation. Neither age at onset nor duration of respiratory distress were different in patients with a mature surfactant phospholipid pattern compared with those with an immature pattern. In addition, chest roentgenograms were similar in both groups of patients.

COMMENT

Although all infants in this report had clinical and radiologic findings similar to those seen in RDS, certain features of their illness (shock, apnea, leukopenia, etc) suggested the presence of infection. This has been previously noted by Ablow et al[18] in early-onset infection with GBS. Also, all patients had chest roentgenograms that were to some extent atypical of RDS and that suggested coexistence of pneumonia.[14,19]

Saunders et al[6] found a mature phospholipid composition of tracheal aspirates in three term infants with early-onset GBS sepsis. Tanswell and Smith[7] and Lewins[8] described a total of seven premature infants with early-onset GBS sepsis who had abnormal "shake tests," suggesting surfactant maturity. Two additional extremely immature infants (27 weeks' gestation) described by Lewins[8] had normal "shake tests," suggesting these infants also had RDS.

Analysis of phospholipids in gastric and tracheal aspirates on the first day of life in the nine patients described here demonstrated that five patients had mature patterns, suggesting that RDS was not present. An additional four patients had immature phospholipid patterns in their tracheal aspirates, suggesting that RDS coexisted with early-onset sepsis and/or pneumonia. Neither the clinical and radiologic presentation nor the outcome differentiated patients whose surfactant phospholipid patterns in tracheal aspirates were mature from those whose were immature. However, the five patients with mature phospholipid patterns were more mature on the basis of estimated gestational age than those with immature phospholipid patterns. Since complete surfactant maturity normally may occur as early as 34 to 35 weeks' gestation,[17] the presence of a mature surfactant complex in these infants may be due to their relatively advanced gestational age.

It has been suggested[7] that an abnormal gastric aspirate "shake test," suggesting maturity of surfactant in a patient with respiratory disease simulating RDS, should be an indication to search for a source of infection and the institution of antibiotic therapy. The presence of a mature phospholipid complex in some of our patients confirms such a recommendation. However, our results suggest that an immature pattern suggesting RDS in preterm infants does not exclude the coexistence of early-onset sepsis and/or pneumonia.

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References

1. Quirante J, Ceballos R, Cassady G: Group B β-hemolytic streptococcal infection of the newborn: I. Early onset infection. *Am J Dis Child* 128:659-665, 1974.

2. Vollman JH, Smith WL, Ballard ET, et al: Early onset group B streptococcal disease: Clinical, roentgenographic, and pathologic features. *J Pediatr* 89:199-203, 1976.

3. Bale JF, Watkins M: Fulminant neonatal *Hemophilus influenzae* pneumonia and sepsis. *J Pediatr* 92:233-234, 1978.

4. Headings DL, Herrera A, Mozzi E, et al: Fulminant neonatal septicemia caused by *Streptococcus bovis*. *J Pediatr* 92:282-283, 1978.

5. Bortolussi R, Thompson TR, Ferrieri PL: Early-onset pneumococcal sepsis in newborn infants. *Pediatrics* 60:352-355, 1977.

6. Saunders BS, Merritt TA, Kirkpatrick E, et al: Group B streptococci in the newborn. *Lancet* 1:1053, 1977.

7. Tanswell AK, Smith BT: The gastric aspirate shake test. *J Engl J Med* 297:1471, 1977.

8. Lewins MJ: The gastric aspirate shake test and group B streptococcal disease. *N Engl J Med* 298:1200, 1978.

9. Bligh EG, Dyer WJ: A rapid method of total lipid extraction and purification. *Can J Bioehcm Physiol* 37:911-912, 1959.

10. Gluck L, Kulovich MV, Borer RC Jr: Estimates of fetal lung maturity. *Clin Perinatol* 1:125-139, 1974.

11. Hallman M, Kulovich M, Kirkpatrick E, et al: Phosphatidylinositol and phosphatidylglycerol in amniotic fluid: Indices of lung maturity. *Am J Obstet Gynecol* 125:613-617, 1976.

12. Wesenberg RL: *The Newborn Chest*. Hagerstown, Md, Harper & Row Publishers, 1973, pp 55-70.

13. Loenidas JC, Hall RT, Beatty EC, et al: Radiographic findings in early onset neonatal group B streptococcal septicemia. *Pediatrics* 59(suppl):1006-1011, 1977.

14. Weller MH, Katzenstein AA: Radiologic findings in group B streptococcal sepsis. *Radiology* 118:385-387, 1976.

15. Hallman M, Feldman BH, Kirkpatrick E, et al: Absence of phosphatidylglycerol (PG) in respiratory distress syndrome in the newborn. *Pediatr Res* 11:714-720, 1977.

16. Obladen M, Merritt TA, Gluck L: Alterations in tracheal phospholipid composition during RDS, abstracted. *Pediatr Res* 10:465, 1976.

17. Kulovich MV, Hallman MB, Gluck L: The lung profile: I. Normal pregnancy. *Am J Obstet Gynecol* 135:57-63, 1979.

18. Ablow RC, Driscoll SG, Effmann EL, et al: A comparison of early-onset group B streptococcal neonatal infection and the respiratory distress syndrome of the newborn. *N Engl J Med* 294:65-70, 1976.

19. Foote GA, Stewart JH: The coexistence of pneumonia and idiopathic respiratory distress syndrome in neonates. *Br J Radiol* 46:504-511, 1973.

The Diagnosis of Phenylketonuria

A Report From the Collaborative Study of Children Treated for Phenylketonuria

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• One hundred ninety-five infants who met diagnostic criteria for enrollment in the Collaborative Study of Children Treated for Phenylketonuria (PKU) underwent a standard three-day challenge with 180 mg/kg/day of phenylalanine for confirmation of diagnosis. A sustained rise in serum phenylalanine levels of greater than 20 mg/dL was observed in 166 infants (85.1%), compatible with the diagnosis of classical PKU. In the remaining 29 infants (14.9%), the serum phenylalanine concentration either did not reach 20 mg/dL or, having achieved this level, subsequently declined below this point by 72 hours. It was agreed that these 29 patients had variant PKU and they were dropped from the Collaborative Study. We recommend that all infants diagnosed as having classic PKU undergo a challenge to confirm the diagnosis and need for continued treatment.

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Phenylketonuria (PKU), an inborn error of metabolism, is characterized in the untreated state by mental retardation and the presence of phenylpyruvic acid in the urine, as described initially by Fölling in 1934.[1] Other workers[2,3] later demonstrated that the serum phenylalanine level was persistently elevated above 15 to 20 mg/dL and that, in addition to phenylpyruvic acid, phenylalanine and its metabolites, particularly orthohydroxyphenylacetic acid (o-HPAA) are found in the urine in greatly increased quantities. These biochemical criteria have been generally accepted as the basis of the diagnosis of classic PKU.

Since the development of newborn screening programs for detection of PKU, a population of variant infants with persistent hyperphenylalaninemia has been identified.[4-6] Biochemically, variant individuals are characterized by serum phenylalanine levels generally below 20 mg/dL, but in the newborn period levels ranging from 20 to 30 mg/dL or higher[4,7] have been observed. The amount of phenylalanine metabolites found in the urine varies considerably, usually reflecting the serum phenylalanine level. Phenylpyruvic acid may be either undetectable or present in large quantities, while o-HPAA is found in moderately increased amounts. The incidence of the PKU variant has been estimated at 1:17,000, and the ratio of variant to classic PKU appears to be almost 1:1 in North America.[8]

Prevention of mental retardation in classic PKU may be achieved by institution of a low phenylalanine diet in early infancy, preferably no later than 2 months of age.[9] Clinically, the variant population follows a normal pattern of intellectual development while receiving a normal diet; restriction of phenylalanine intake not only is of no proved benefit to these individuals,[10,11] but may be hazardous to their physical and mental development when inappropriately prescribed.[12] Reported complications associated with the phenylalanine-restricted diet include anorexia, anemia, hypoproteinemia, and hypoglycemia,[13] and it is therefore critically important that all infants with hyperphenylalaninemia be carefully evaluated before committing them to long-term therapy. It is generally agreed that infants with serum phenylalanine levels above 20 mg/dL should be given a phenylalanine-restricted diet, with some centers recommending 15 mg/dL as the appropriate level at which to start treatment.

The biochemical overlap between variant and classic PKU patients is substantial, making differential diagnosis difficult. Attempts to distinguish between the two groups have concentrated on differing responses to a standard load of phenylalanine. The phenylalanine tolerance test developed by Hsia et al[14] to detect the heterozygote state has not been found to be reliable for this purpose, but when phenylalanine is given in the form of a balanced protein load (such as evaporated or whole milk) over an extended period, the two groups can be distinguished[15] by evaluation of the change in serum phenylalanine level observed during the test period. Relatively few individuals have been found to be unclassifiable using this method.[7]

In 1967, the Collaborative Study of Children Treated for Phenylketonuria, representing 19 PKU clinics, began a controlled prospective study to determine the effects of treatment on classic PKU.[16] It was imperative that a pure sample of PKU patients uncontaminated by variant individuals be entered into the study, and accordingly the following criteria were proposed and adopted: (1) Serum phenylalanine levels must have reached or exceeded 20 mg/dL on at least two occasions 24 hours apart while the patients ingested a normal diet for age; (2) serum tyrosine levels, on two specimens obtained at the same time as those for phenylalanine determinations, must have been recorded as no higher than 5.0 mg/dL; and (3) the urinary metabolites found in classic PKU, such as o-HPAA and phenylalanine itself, must have been present in excess.

As the possibility existed that some variants would meet these criteria initially, the protocol called for confirmation of the diagnosis of all subjects

From the Collaborative Study of Children Treated for Phenylketonuria. For a complete list of project staff and participating clinics, see p 744.

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three months after tentative diagnosis and initiation of treatment by means of a standardized challenge procedure.[17] If, in response to the challenge, the serum phenylalanine level exceeded 20 mg/dL for 24 hours or longer and the urine at that time contained increased amounts of the metabolites found in classic PKU, the subject was considered to have true PKU and continued in the treatment phase of the study at the discretion of the clinic director.

The purpose of this report is to describe the experience of the Collaborative Study of Children Treated for Phenylketonuria in using these criteria for the diagnosis of PKU.

PATIENTS AND METHODS

Biochemical Studies

All serum phenylalanine determinations were performed by means of the McCaman-Robins[18] fluorometric method. Serum tyrosine levels were determined by the fluorometric method of Waalkes and Udenfriend.[19] Aliquots of samples obtained at the time of diagnosis and phenylalanine challenge were sent to the Serum Reference Laboratory at the University of Southern California, Los Angeles, for comparability of results of serum phenylalanine and tyrosine. Urine collected at the times of diagnosis and challenge was acidified to pH 1.8 ± 0.2 and sent to the Chromatographic Reference Laboratory at the same institution for determination of creatinine, phenolic acid, and ferric chloride levels and two-dimensional paper chromatography for phenylalanine metabolites. (Variations above and below mean values are SDs, not SEMs.)

Phenylalanine Challenge

Three months after institution of therapy, the need for continuation of the restricted diet was evaluated by means of a natural protein challenge. This procedure involved discontinuation of the low phenylalanine (Lofenalac) diet; in its place, 720 mL of whole milk or 360 mL of evaporated milk diluted with 360 mL of water was given every 24 hours. After experience, the amount of milk offered was adjusted individually to provide an intake of 180 mg/kg/day of phenylalanine for each infant. The milk was offered in frequent small feedings spaced throughout the day to minimize loss by emesis. Water intake was encouraged during the challenge period. A high-carbohydrate, nonprotein supplement (Dextri-Maltose), was used freely to ensure a good caloric intake. The challenge was performed only when the infant was in good health, since even minor illnesses may cause elevations in serum phenylalanine levels, thus potentially leading to misdiagnosis.

The protocol required that the challenge be continued for 48 to 72 hours. For the first years of the study, serum phenylalanine values were usually obtained only at the end point. However, as experience with the procedure was gained, determinations were requested at intervals of 24 ± 4 hours and the challenge was extended to 72 hours.

Initially, if the serum phenylalanine level was known with certainty to exceed 20 mg/dL prior to 72 hours, it was considered acceptable to discontinue the challenge early. Two urine samples were collected for determination of phenylalanine and metabolites—the first prior to and the second at 60 to 72 hours after the initiation of the procedure.

For those patients in whom the challenge was delayed beyond infancy, frequently because of intercurrent illness at the time the challenge was scheduled, a similar protocol was followed using phenylalanine (L-phenylalanine) as an alternative to natural protein. It was suggested that the ingestion of large quantities of natural protein by older children over a three-day period might be unpredictable. No change was made in the basic dietary prescription, but the phenylalanine content of the diet was increased to 180 mg/kg/day by the addition of phenylalanine to the low phenylalanine formula in calculated amounts. Blood and urine samples were obtained as already described.

Patient Selection

Infants admitted to the Collaborative Study were born between Oct 1, 1967, and Sept 30, 1972, in states with newborn screening programs for detection of PKU. In addition to meeting the biochemical criteria listed in an earlier section, it was required that infants be less than 120 days of age at the time of entry. The protocol was discussed with parents, and informed consent was obtained prior to enrollment of their child in the study.

RESULTS

Two hundred twenty-four infants entered the project as index patients. All but eight of these met study criteria, giving a total of 216 infants—124 boys and 92 girls—formally enrolled. Most of the infants were born at term (only 8.8% of the 182 infants for whom gestation was recorded being born at less than 38 weeks' gestation); 96.8% were white, and 49.6% were first-born.

Initial Data

Serum biochemistry determinations were obtained for 216 infants on entry to the study, when their mean age was 20.7 ± 14.5 days. The serum phenylalanine levels ranged from 20.7 to 98.4 mg/dL, resulting in a mean value for the group of 45.1 ± 14.8 mg/dL.

Data on serum tyrosine levels were available on 193 subjects (89.4%), the mean value being 2.4 ± 1.1 mg/dL. Individual values ranged from 0.6 to 6.7 mg/dL. Six infants had levels above 5 mg/dL; subsequently, however, the levels declined to below 5 mg/dL. One infant of 36 weeks' gestation was initially thought to have transitory neonatal tyrosinemia, and the diagnosis of PKU was made when the serum tyrosine level was noted to decline whereas the phenylalanine level remained above 20 mg/dL.

There was no significant difference in values of serum phenylalanine and tyrosine for males and females.

Urinary metabolites were measured in samples obtained from 181 patients (83.8%); phenylalanine and o-HPAA values were elevated above the upper limit of normal (100 mg of phenylalanine per gram of creatinine and 1 mg of o-HPAA per gram of creatinine) in all the infants.

Challenge Data

The protocol called for the challenge to be performed three months after tentative diagnosis and institution of therapy, which occurred at a mean age of 22.4 ± 14.8 days for the group (range, 3 to 92 days of age). Fifteen subjects were not challenged for various reasons (family and/or clinic noncompliance with the protocol, family move to an area without a participating clinic, etc) and were dropped from the study.

Challenge data from 201 patients (93.0%) were available for analysis. However, the limited requirement for blood samples and dietary information during the first years of the study rendered some procedures inadequate for complete evaluation. Additionally, the decision by participants to discontinue the challenge once the phenylal-

Table 1.—Mean Phenylalanine Intake and Serum Levels During Challenge (N = 67)

	Type 1 Response (N = 45)		Type 2 Response (N = 7)		Type 3 Response (N = 15)	
	24-hr Phenylalanine Intake, mg/kg	Serum Phenylalanine, mg/dL	24-hr Phenylalanine Intake, mg/kg	Serum Phenylalanine, mg/dL	24-hr Phenylalanine Intake, mg/kg	Serum Phenylalanine, mg/dL
Baseline						
Mean	...	6.8	...	7.4	...	4.3
SD	...	4.4	...	3.2	...	2.7
N	...	36*	...	6	...	14
24 hr†						
Mean	176	24.0	176	21.2	173	13.2
SD	32.0	8.1	32.0	4.0	36.3	3.9
N	45	45	7	7	15	15
48 hr†						
Mean	190	37.3	188	18.9	173	14.1
SD	33.8	9.6	30.7	6.1	40.1	3.5
N	44	45	7	7	15	15
72 hr						
Mean	194	43.6	186	14.6	181	13.1
SD	81.3	9.6	26.4	3.9	54.3	5.7
N	41	45	7	7	15	15

*Differences between populations reflect missing data.
†± 4 hours.

anine level exceeded 20 mg/dL led to many abbreviated procedures. Ninety-four procedures (46.7%) continued for 72 hours, while 99 (49.2%) were terminated at various other times (24 hours, 10 patients; 36 hours, 6; 48 hours, 48; 60 hours, 32; more than 72 hours, 3). The remaining eight patients (3.9%) underwent initial challenge with phenylalanine at a mean age of 30.1 ± 18.3 months.

Sixty-seven challenges in which natural protein was administered for 72 hours and serum phenylalanine determinations were obtained at 24, 48, and 72 ± 4 hours are described here. There were 36 boys and 31 girls in this group, ranging in age from 2.2 to 20.7 months at the time of challenge (mean age, 4.8 ± 2.7 months), representing 33.3% of the total challenges performed. Two patients who met the criteria for a complete challenge were dropped from the study at the discretion of the clinic director and are excluded from this analysis.

All infants were physically well at the beginning of the challenge, but two subsequently had fever, which was described as "transient" and "slight" and required no therapy during the procedure. Three infants refused to ingest the prescribed amount of formula; in one of these, the difficulty appeared to be related to mild nasal discharge. Slight irritability was recorded in a single infant. The most common problem was minimal vomiting or spitting up, recorded in ten infants. One infant was gavage fed to ensure adequate intake. In all, 16 infants (5 boys, 11 girls), representing 23.9% of the group, had problems of this nature.

Three types of responses were observed in the serum biochemistry studies (Table 1):

1. Forty-five patients (67.2%) demonstrated a sustained and continuous rise in serum phenylalanine level over the challenge period. In all 45 patients, the highest serum phenylalanine level was recorded at 72 hours (type 1 response). The mean serum phenylalanine level for this group was above 20 mg/dL at 24, 48, and 72 hours. Of the 23 male and 22 female infants in this group, 11 suffered minor physical problems with the procedure: vomiting, 3 boys and 3 girls; refusal of some of the prescribed formula, three girls; slight irritability, one boy; and slight fever, one girl. There was no significant difference between the rate of rise of serum phenylalanine for male and female infants.

2. Seven patients (10.4%) demonstrated a rise of serum phenylalanine level of greater than 20 mg/dL at 24 hours or 48 hours or both after institution of the challenge, but a subsequent decline occurred by 72 hours to less than 20 mg/dL in all, despite continuation of the procedure (type 2 response). Of the four boys and three girls with this response, one boy had transient fever and one girl had minimal vomiting.

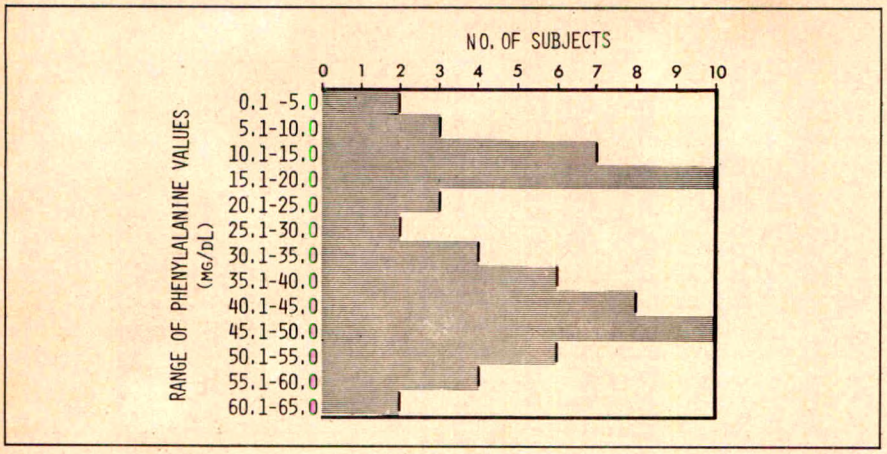
3. Fifteen infants (22.4%) failed to demonstrate a rise in serum phenylalanine level above 20 mg/dL at any point in the challenge procedure (type 3 response). Nine boys and six girls demonstrated this response, of whom three (all female) suffered minimal vomiting during the procedure.

The phenylalanine intake during the challenge was calculated in milligrams per kilogram for each 24-hour period of the procedure (Table 1). There was no statistically significant difference in the amount ingested by patients with types 1, 2, or 3 responses.

Urinary metabolites were measured in samples from 65 of the 67 subjects. Phenylalanine and o-HPAA levels in excess of normal amounts were found in all postchallenge specimens.

Interpretation of Challenge Data

The serum phenylalanine levels in patients with type 2 and 3 responses differed significantly at 0 hours ($P = .02$), 24 hours ($P < .001$), and 48 hours ($P = .02$). At 72 hours, however, there was no significant difference between the two groups. In contrast, the serum phenylalanine determinations of type 1 patients were significantly different at 48 and 72 hours



Frequency distribution of 72-hour phenylalanine levels in 67 patients undergoing natural protein challenge.

Table 2.—Mean Maximum Initial Serum Phenylalanine Levels in Patients With Classic and Variant Challenge Response

	Classic (N = 45)	Variant (N = 22)	*P*
Initial serum phenylalanine, mg/dL	47.4 ± 14.4	30.7 ± 9.3	< .001
Range, mg/dL	23.1 — 85.0	21.0 — 59.9	. . .
Age, days	21.0 ± 16.2	26.1 ± 14.8	NS
Sex, M/F ratio	1:0.95	1:0.70	NS

Table 3.—Mean Serial Serum Phenylalanine Levels Obtained in Challenges

	Mean Serum Phenylalanine, mg/dL		
Time, hr	Complete Challenges (Classic Response) (N = 45)	Incomplete Challenges (N = 111)	L-Phenylalanine Challenges (N = 8)
24 ± 4	23.9 ± 8.1 (45*)	31.5 ± 5.5 (10)	28.8 (1)
37.5 ± 4.6	. . .	37.5 ± 4.6 (6)	. . .
48 ± 4	37.3 ± 10.0 (45)	39.0 ± 8.2 (45)	32.2 ± 8.3 (4)
61.5 ± 4.6	. . .	38.8 ± 9.1 (29)	. . .
72 ± 4	43.6 ± 9.6 (45)	36.4 ± 12.4 (19)	32.0 ± 3.6 (3)
76	. . .	40.7 ± 11.7 (2)	. . .

*No. of cases.

when compared with those of both types 2 and 3 ($P < .001$ at each time).

When Type 2 and 3 data were analyzed so as to take the difference at 0 hours between the two groups into account, no significant difference was noted. On review of the distribution of the 72-hour phenylalanine levels for all 67 subjects (Figure), two distinct peaks in the 15.1-to-20-mg and 45.1-to-50-mg ranges were noted, supporting the assumption of two distinct populations of subjects. It was therefore agreed that type 2 and 3 responses were characteristic of the individual with variant PKU, and the challenge data of the 22 patients with these responses were pooled, resulting in a pattern considered typical of variant status. While these represent one third of the individuals with complete challenges, it should be emphasized that this incidence is higher than if the whole sample had been available for similar review. Decisions to terminate challenge once serum phenylalanine levels rose above 20 mg/dL tended to reduce the number of procedures lasting 72 hours. In contrast, the slower rise and relatively low levels achieved by the variant individuals led to a greater number of complete procedures.

Review of Variant Status

The initial presentation and course following study discontinuation of these 22 patients with a variant response were reviewed.

Diagnostic Data.—Table 2 lists the mean maximum initial phenylalanine levels for variant and classic PKU patients, together with ranges and SDs. The difference between the 45 classic PKU patients and the 22 variant individuals is highly significant ($P < .001$). There was no significant difference in age and sex between the two groups.

Despite the large difference between the means, it should be noted that the overlap of the values in the two groups limits the usefulness of these data in terms of initial diagnosis.

Course Following Discontinuation From Study.—Decision as to further management of these variant patients differed, reflecting the clinic directors' views of hyperphenylalaninemia, the parent's wishes, and, frequently, the results of further challenges. In general, dietary management was less restricted or discontinued, a formal PKU diet being continued in only one patient. Twelve infants resumed a completely normal diet between 3 and 15 months of age. Two of these, male siblings, were found to suffer from dihydropteridine reductase deficiency and are described elsewhere.[20] The remaining nine patients continued to receive a low phenylalanine diet until 12 to 24 months of age, when the diet was modified by allowing solid foods at will while continuing the low phenylalanine formula. Two of these nine resumed a normal diet at 3 years of age. Mean serum phenylalanine levels in these children once the diet was relaxed or discontinued ranged from 3.1 to 18.4 mg/dL. In no case was it considered necessary to resume a formal phenylalanine-restricted diet on the basis of either persistent serum phenylalanine levels above 20 mg/dL or clinical findings.

The results of follow-up intelligence testing are available for 15 of the 22 variant patients. Their mean IQ on the Stanford-Binet test (1960 norms) was recorded as 102 ± 15, compared with a mean IQ of 103 ± 14 on the

same test for 44 of the 45 patients classified as having classic PKU.

Thus, the variant individuals identified in this study may be characterized as having an initial serum phenylalanine level above 20 mg/dL in early infancy, compatible with the diagnosis of classic PKU. However, 72 hours after institution of a natural protein challenge in later infancy and on resumption of a normal diet, the serum phenylalanine level is persistently recorded as below 20 mg/dL.

Incomplete Challenges

There were 124 patients whose challenges with natural protein were considered incomplete either as to length of procedure or lack of blood sampling at 24, 48, or 72 hours. To determine the status of these patients, the final serum phenylalanine level obtained in each case in which the decision had been made to discontinue the challenge was selected for analysis and comparison with the serial data obtained from those who had complete studies.

One hundred fifteen infants had final serum phenylalanine levels above 20 mg/dL. Four of these were dropped from the study at the discretion of the clinic director and are excluded from the presentation. Table 3 presents the data from the remaining 111 infants, compared with the serial data obtained from the 45 patients with classic PKU described previously. The mean serum phenylalanine value recorded prior to 72 hours substantiates the reasoning behind early discontinuation of the challenge in these cases, particularly at 24 hours. There is no significant difference between these groups, and the diagnosis of classic PKU in these 111 patients appears to be clear.

There were nine patients whose final serum phenylalanine level was reported to be below 20 mg/dL. One, whose phenylalanine intake during the challenge averaged only 108 mg/kg/day, underwent a later procedure with *l*-phenylalanine (average intake, 187 mg/kg/day) and achieved a 72-hour serum level of above 20 mg/dL. The remaining eight patients were given less restricted or normal diets; all but one maintained phenylalanine levels below 20 mg/dL. This exception, a patient for whom dietary information during the challenge was inadequate, had a phenylalanine level above 30 mg/dL and was considered to have classic PKU. These two patients were continued in the study as subjects. Table 4 demonstrates the final serum phenylalanine levels of the remaining seven patients compared with the serial levels obtained in the 22 variant patients described previously. There is no statistically significant difference between these groups, and these seven responses are considered compatible with the variant state.

Table 4.—Final Serum Phenylalanine Levels < 20 mg/dL in Subjects With Incomplete and Complete Challenges

Time, hr	Mean Serum Phenylalanine, mg/dL: Complete Challenges (Variant Response) (N = 22)	Mean Serum Phenylalanine, mg/dL: Incomplete Challenges (N = 7)
24 ± 4	15.7 ± 5.3 (22*)	. . .
48 ± 4	15.6 ± 4.9 (22)	. . .
61 ± 4.6	. . .	16.0 ± 2.5 (2)
72 ± 4	13.5 ± 5.2 (22)	15.3 ± 3.3 (4)
> 76	. . .	14.1 (1)

*No. of cases.

Table 5.—Classification of 195 Study Patients Into Classic and Variant Phenylketonuria (PKU)*

Method of Classification	Classic PKU	Variant PKU
Natural protein challenge		
Complete	45	22
Incomplete	111	7
Phenylalanine (L-phenylalanine) challenge	8	0
Return to normal diet (temporary	1	0
Second phenylalanine challenge	1	0
Total	**166** (85.1%)	**29** (14.9%)

*Of 216 patients initially admitted to the study, 201 underwent challenge. Six were dropped from the study by the clinic director.

L-Phenylalanine Challenges

The final serum phenylalanine levels in the eight patients undergoing phenylalanine challenge were all above 20 mg/dL (Table 3). Although interpretation of phenylalanine challenges may be difficult,[21] the pattern seen in these patients is compatible with classic PKU.

Classification of the Study Subjects

Table 5 summarizes the classification of the study patients' diagnoses into classic and variant PKU. It can be seen that 29 (14.9%) of the 195 infants were categorized as having variant PKU, all of whom were dropped from the study. The remaining 166 patients (85.1%) appear to fulfill criteria for classic PKU, and the study participants agreed they should continue as subjects.

COMMENT

In the early years of PKU screening, it was generally believed that any serum phenylalanine level above normal was synonymous with actual or potential mental retardation, regardless of the degree of elevation. Thus, some early case reports describe patients with modest elevations of 6 to 12 mg/dL diagnosed as having PKU and treated. Other, usually older children were described as suffering from atypical PKU in view of normal intellectual development without treatment despite serum phenylalanine levels in that range. When newborn screening programs unexpectedly detected a greater number of infants with elevated serum phenylalanine levels than would have been predicted on the basis of the known incidence of PKU, it became clear that a variant of PKU existed that had a vastly different prognosis for intellectual development.

At the time the Collaborative Study Protocol was being developed in 1966 and 1967, knowledge of the variant state was limited but adequate enough to assure the adoption not only of stringent criteria for entry into the study but also of a later phenylalanine challenge to confirm the diagnosis. The value of the challenge is clear: the diagnosis in almost 15% of infants admitted to the study proved to be incompatible with classic PKU. While this incidence is lower than anticipated on the basis of recent data,[8] it can largely be accounted for by the study admission requirement that each subject have serum phenylalanine levels of 20 mg/dL or greater, thus leading to exclusion of the larger population of hyperphenylalaninemic patients with lower levels. A minor factor affecting the incidence may be the use of the 20-mg/dL level as the challenge criterion. This may be too stringent and a few variant subjects may remain undetected in the study population.

Few would question the institution of therapy for patients with a mean serum phenylalanine level of 30 mg/dL early in life; however, continuation of treatment on the basis of the initial data alone must be considered questionable for many. Although no infant in this study had serious problems related to a restricted diet, continuation of such restriction has potential hazards. The emotional cost to the family responsible for maintaining the PKU diet is considerable, and the cost of providing low phenylalanine formula over several years cannot be ignored. Genetic counseling given initially to these families dealt primarily with classic PKU; although variant hyperphenylalaninemia is also inherited as an autosomal recessive characteristic, the prognosis for subsequent offspring differs considerably from that for those with classic PKU.

In practice, the variant state may be suspected by a more rapid decline in serum phenylalanine levels following introduction of treatment than is usually seen in classic PKU. Information on this point is episodic and is influenced by the various methods of introducing treatment in different clinics.[22] Additionally, variant patients may show a greater tolerance for phenylalanine than that seen in the classic individual, which is most marked in later infancy and childhood. Individual variations between infants in requirements for phenylalanine may be great,[17] but this difference may not be evident in the first few weeks of life. The use of a standard challenge appears to be a reliable method to determine variant status and is recommended for use in all infants diagnosed as suffering from PKU.

The milk challenge described here proved easy to perform in many different clinics both on an inpatient and outpatient basis. The morbidity was minor and the gains to the patient were unquestionable. Had this procedure not been performed, not only would 29 children have been continued on rigorous dietary restriction without proved benefit, but the study population would have been contaminated, with approximately one of six of its patients likely to do well intellectually without treatment.

The Project Staff of the Collaborative Study of Children Treated for Phenylketonuria include the following: Richard Koch, MD, *Medical Director*, 1967-1975, 1976-present; George Donnell, MD, *Medical Director*, 1975-1976; Malcolm L. Williamson, PhD, *Project Co-director;* James C. Dobson, PhD, *Project Co-director*, 1967-1977; Eva Gross Friedman, *Project Coordinator*. The following clinics participated in this study: Oregon State Board of Health, Portland; University of Wisconsin Medical Center, Madison; Children's Hospital of Los Angeles; Children's Memorial Hospital, Chicago; Children's Medical Center, Tulsa, Okla; Milwaukee Children's Hospital; University of Colorado, Denver; University of Washington, Seattle; Loyola University School of Medicine, Maywood, Ill; Children's Hospital and Health Center, San Diego; University of Illinois Hospital, Chicago; Chicago Medical School; University of Texas, Medical School Branch, Galveston; State University of New York, Syracuse; University of Miami (Fla); University of Iowa, Iowa City; University of Maryland School of Medicine, Baltimore; State Department of Health, Baltimore; Johns Hopkins Hospital, Baltimore; Children's Hospital, Buffalo; and University of Nebraska, Omaha. Samuel Bessman, MD, and Kenneth N. F. Shaw, PhD, served as Laboratory Directors.

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Mildred Schafer typed the manuscript.

References

1. Fölling A: Uber ausscheidung von phenylbrenztraubensäure in den harn als stoffwechselanomalie in verbindung mit imbezzillität. *Z Physiol Chem* 227:169-176, 1934.

2. Jervis GA, Block RJ, Bolling D, et al: Phenylalanine content of blood and spinal fluid in phenylpyruvic oligophrenia. *J Biol Chem* 134:105-113, 1940.

3. Armstrong MD, Low ML: Phenylketonuria: VIII. Relation between age, serum phenylalanine level and phenylpyruvic acid excretion. *Proc Soc Exp Biol Med* 94:142-146, 1957.

4. Justice P, O'Flynn ME, Hsia DYY: Phenylalanine hydroxylase activity in hyperphenylalaninemia. *Lancet* 1:928-929, 1967.

5. Berman JL, Cunningham GC, Day RW, et al: Causes for high phenylalanine with normal tyrosine. *Am J Dis Child* 117:54-65, 1969.

6. Cunningham GC: Phenylketonuria testing: Its role in pediatrics and public health. *CRC Crit Rev Clin Lab Sci* 2:45-101, 1971.

7. Blaskovics ME, Schaeffler GE, Hack S: Phenylalaninaemia: Differential diagnosis. *Arch Dis Child* 49:835-843, 1974.

8. Newborn screening for metabolic disorders, Massachusetts Department of Public Health. *N Engl J Med* 288:1299-1300, 1973.

9. Dobson J, Koch R, Williamson M, et al: Cognitive development and dietary therapy in phenylketonuric children. *N Engl J Med* 278:1142-1144, 1968.

10. Berman JL, Ford R: Intelligence quotients and intelligence loss in patients with phenylketonuria and some variant states. *J Pediatr* 77:764-770, 1970.

11. Levy HL, Shih VE, Karolkewicz V, et al: Persistent mild hyperphenylalaninemia in the untreated state. *N Engl J Med* 285:424-429, 1971.

12. Rouse BM: Phenylalanine deficiency syndrome. *J Pediatr* 69:246-249, 1966.

13. Hanley WB, Linsao LS, Davidson W, et al: Malnutrition with early treatment of phenylketonuria. *Pediatr Res* 4:318-327, 1970.

14. Hsia DYY, Driscoll KW, Troll W, et al: Detection of the heterozygous carrier for phenylketonuria by phenylalanine tolerance tests. *Nature* 178:1239-1240, 1956.

15. Blaskovics ME, Shaw KNF: Hyperphenylalaninemia: Methods for differential diagnosis, in Bickel H, Hudson FP, Wolf LI (eds): *Phenylketonuria*. Stuttgart, West Germany, Georg Thieme Verlag, 1971, pp 98-102.

16. Williamson M, Dobson JC, Koch R: Collaborative Study of Children Treated for Phenylketonuria: Study design. *Pediatrics* 60:815-821, 1977.

17. Shaw RNF, Koch R, Donnell GN, et al: *Management of Infants With Phenylketonuria*, publication 78. US Dept of Health, Education, and Welfare, 1978, p 5211.

18. McCaman MW, Robins E: Fluorometric method for the determination of phenylalanine in serum. *J Lab Clin Med* 58:885-890, 1962.

19. Waalkes TP, Udenfriend S: A fluorometric method for estimation of tyrosine in plasma and tissues. *J Lab Clin Med* 50:733-738, 1957.

20. Milstein S, Holtzman NA, O'Flynn ME, et al: Hyperphenylalaninemia due to dihydropteridine reductase deficiency. *J Pediatr* 89:763-766, 1976.

21. Blaskovics ME: Diagnostic considerations in phenylalaninemic subjects before and after dietary therapy. *J Ir Med Assoc* 69:410-414, 1976.

22. Acosta PB, Wenz E, Williamson M: Methods of dietary inception in infants with PKU. *J Am Diet Assoc* 72:164-169, 1978.

The String Test for Gastroesophageal Reflux

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• The sensitivity of the string test for detection of gastroesophageal reflux was assessed in 15 infants and children, 5 months to 11 years of age (mean, 2.8 years), with vomiting, regurgitation, or lower respiratory tract symptoms, and compared with the barium esophagram, esophageal manometry, and the acid reflux test (pH probe). Barium esophagram showed reflux in 4/15 patients, pH probe in 7/15, and string test in 6/15. The string test is a simple, rapid, safe, and efficient screening method for patients with suspected gastroesophageal reflux.
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Vomiting is one of the most frequent problems confronting the pediatrician. The predominant mechanism implicated in most cases has been gastroesophageal reflux (GER), vomiting being its most frequent symptom.[1-4] The present study was undertaken to evaluate the sensitivity of the string test (Gastro-Test), a simple, accurate technique, in detection of GER in comparison to the barium esophagram, esophageal manometry, and acid reflux test (pH probe).[5]

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PATIENTS AND METHODS

Fifteen infants and children (5 months to 11 years, mean, 2.8 years; six males and nine females) with recurrent vomiting, regurgitation, or recurrent lower respiratory tract symptoms were evaluated for GER. The string test, esophageal manometry, and the acid reflux test were performed on the same day. Sedation (meperidine hydrochloride [Demerol] and promethazine hydrochloride [Phenergan], 1 mg/kg, parenterally) was used in patients younger than 5 years of age. All patients were fasted for at least six to eight hours. The string test was also performed in 45 infants and children (5 months to 15 years; 24 males and 21 females) with chronic diarrhea of undetermined cause. Informed consent was obtained in all patients.

Measurement of lower esophageal sphincter pressure was performed as described by Arndorfer.[6] The acid reflux test was accomplished by use of the microcecar combination electrode as described by Euler et al.[1,2] Reflux was established when a pH of 3 or less on two occasions (15 s or more per episode) was recorded in the supine, prone, right, or left lateral positions. Spontaneous and induced reflux were evaluated before and after introduction of 0.1N hydrochloric acid into the stomach (300 mL/1.73 sq m body surface area).[1-4] The acid was aspirated at the end of the procedure.

The string test (Gastro-Test used for those older than 2 years of age and Entero-Test-Pediatric (for those younger than 2 years) was performed on all patients. After a six- to eight-hour fast, the patient swallowed the capsule with water, or the capsule was placed in the posterior pharynx and then swallowed. The free end of the string was taped to the cheek and normal activity was resumed. After 15 minutes, the string was pulled out and examined. The distance (centimeters) from the incisors to any area with color indicative of a pH of less than 3.0 was measured. Approximate anatomic correlation was recorded.[5]

Barium esophagram was performed on all patients with suspected GER. The presence or absence of reflux was assessed, as was the level of reflux.

RESULTS

Seven patients (47%) had positive acid reflux tests and six (38%) positive string tests. Acid reflux was confirmed at both a 15- and 20-cm distance from the incisors in the six patients with positive string tests.

Lower esophageal sphincter (LES) pressures were measured in all patients without incident. Lower esophageal sphincter pressure (mean ± SD) was significantly less in the seven patients with reflux in comparison with eight without reflux (14.1 ± 1.11 mm Hg vs 19.2 ± 1.11 mm Hg, respectively, $P < .025$). Barium esophagram showed reflux in four of 15 patients. Of eight patients

without acid reflux, all had normal roentgenographic examinations. Of seven patients with acid reflux by pH probe and six by string test, four had reflux demonstrated by barium examination. The string test was negative in all of the 45 patients with diarrhea.

COMMENT

Recent studies have confirmed the sensitivity of the acid reflux test in establishing GER.[1,2,4,7] Furthermore, the acid reflux test has been found to be superior to the barium esophagram in diagnosing GER.[1,4] Our percentage of positive barium examinations for GER were comparable to that of Christie,[4] while being considerably higher than that reported by Euler and Ament,[1,2] and lower than some roentgenographic investigators have reported.[3,8]

More recently, a promising technique for demonstrating and quantitating GER has been developed that involves ingestion of technetium TC 99m sulfur colloid and subsequent scanning of the gastroesophageal area.[9] This scintiscan procedure does expose the patient to a small amount of radiation and requires special equipment. Correlation with the pH probe test has been good.[9,10] Another new technique, for detection of GER involves the use of methylene blue.[11,12] This test does involve the use of a nasogastric tube for insertion of methylene blue in 0.1N hydrochloric acid into the stomach, as well as placement of a polyvinyl tube with multiple openings and cotton thread inside to detect staining with methylene blue. This tube was kept in place in the lower esophagus for as long as two hours in the initial studies.[11,12] The correlation with results of the barium examination and with the pH probe test has been good.[11,12] The present study has demonstrated the string test to be rapid, accurate, inexpensive, and safe in all age groups. The correlation with the acid reflux test is excellent, and in addition, the capability of approximate localization of reflux during the same test period without need for the use or relocation of any instrument, any radiation exposure, or potential complications makes it particularly attractive as a screening test for patients with suspected GER.

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References

1. Euler AR, Ament ME: Gastroesophageal reflux in children: Clinical manisfestations, diagnosis, pathophysiology, and therapy. *Pediatr Ann* 5:22-43, 1976.
2. Euler AR, Ament ME: Detection of gastroesophageal reflux in the pediatric-age patient by esophageal intraluminal pH probe measurement (Tuttle test). *Pediatrics* 60:65-68, 1977.
3. Darling DB, Fisher JH, Gellis SS: Hiatal hernia and gastroesophageal reflux in infants and children. *Pediatrics* 54:450-455, 1974.
4. Christie DL: The acid reflux test for gastroesophageal reflux. *J Pediatr* 94:78-81, 1979.
5. Liebman WM: Tests for gastroesophageal reflux. *Lancet* 2:787, 1978.
6. Arndorfer RC, Stef JJ, Dodds WJ, et al: Improved infusion system for intraluminal esophageal manometry. *Gastroenterology* 73:23-27, 1977.
7. Behar J, Bianciani P, Sheahan DG: Evaluation of esophageal tests in the diagnosis of reflux esophagitis. *Gastroenterology* 71:9-15, 1976.
8. McCauley RGK, Darling DB, Leonidas JC, et al: Gastroesophageal reflux in infants and children: A useful classification and reliable physiologic technique for its demonstration. *Am J Roentgenol* 130:47-50, 1978.
9. Fisher RS, Malmud LS, Roberts GS, et al: Gastroesophageal (GE) scintiscanning to detect and quantitate GE reflux. *Gastroenterology* 70:301-308, 1976.
10. Christie DL, Rudd TG: Radionuclide test for gastroesophageal Reflux (GER) in children. *Pediatr Res* 12:432, 1978.
11. Girardi G, Vial L, Fritis E, et al: Diagnosis of gastroesophageal reflux in infants and children by methylene-blue test. *Lancet* 1:1236-1237, 1978.
12. Christie DL: Methylene-blue test for gastroesophageal reflux. *Lancet* 2:474, 1978.

Girl Shucking Oysters; Gulf Coast Canneries

Lewis W. Hine

From the International Museum of Photography, Rochester, NY

Rotavirus Gastroenteritis in the Washington, DC, Area

Incidence of Cases Resulting in Admission to the Hospital

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• The incidence of rotavirus gastroenteritis in infants and children that required admission to the hospital was estimated for a defined population of approximately 105,000 individuals, including 29,000 children aged 15 years or younger whose primary health care was provided by Group Health Association, Inc, a health maintenance organization in the Washington, DC, area. From January 1977 through March 1979, almost all infants and children in this age group who required hospitalization for gastroenteritis were studied for evidence of infection with human rotavirus (HRV) and other agents. On the average, one in 272 (3.7/1,000) infants less than 12 months old and one in 451 (2.2/1,000) children aged 13 through 24 months were hospitalized for HRV disease each winter. The incidence of rotavirus gastroenteritis requiring hospitalization declined precipitously in children after the second birthday and such illness was not detected in children aged 5 years or older. The role of other agents in acute gastroenteritis requiring hospitalization was minimal, compared with that of rotavirus.

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Human rotavirus (HRV) has proved to be the major etiologic agent of serious acute gastroenteritis in infants and children less than 2 years old wherever this disease has been studied throughout the world.[1-4] The importance of HRV as a cause of such gastroenteritis has been ascertained primarily in studies of infants and children hospitalized with this disease.[1-5] However, in such studies, incidence rates of hospitalization caused by HRV infection could not be derived since it was not possible to define precisely the population from which the hospitalized patients came. In an attempt to obtain such rates, we undertook a study of the incidence of pediatric HRV gastroenteritis in a well-defined pediatric population whose medical care is provided by Group Health Association, Inc (GHA), a health maintenance organization in the Washington, DC, metropolitan area. Almost all hospitalizations of children enrolled in the GHA occurred at our hospital.

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PATIENTS AND METHODS

The GHA serves individuals at varied income levels in government and private industry in the Washington, DC, area and utilizes Children's Hospital National Medical Center (CHNMC) as its hospital for pediatric admissions. The average family enrolled in GHA has 3.8 members, and a demographic profile of these individuals closely resembles that of the total population of the District of Columbia (unpublished information, Group Health Association, Inc, Washington, DC, 1978). The total population served by the GHA numbers approximately 105,000 and about 28% of these are younger than 15 years old. Approximately one third of the families reside in areas closely adjacent to the

Incidence of Gastroenteritis (GE) by Age and Severity

Category	Age: ≤ 12 mo			13- ≤ 24 mo			25- ≤ 60 mo			61 mo- ≤ 15 yr			Total (< 1- < 15 yr)		
	1977	1978	1979*	1977	1978	1979*	1977	1978	1979*	1977	1978	1979*	1977	1978	1979*
No. of individuals at risk	1,232	968	1,064	1,078	1,350	1,176	5,803	5,696	5,058	21,143	21,094	20,718	29,256	29,108	28,016
Treatment incidence No. with GE requiring outpatient clinical care	154	127	...	369	361	...	137	123	...	314	263	...	974	874	...
No. hospitalized with GE	3	11	7	3	2	5	1	0	2	1	2	1	8	15	15
No. hospitalized with rotavirus GE†	1	5	6	3	1	4	1	0	2	0	0	0	5	6	12
Incidence of rotavirus GE necessitating hospitalization (No. with illness/1,000/yr)		3.68			2.22			0.18			0			0.27	

*Includes only January through March. Outpatient visit data for complete 12-month period are not available (indicated by ellipses).
†Rotavirus was detected in the stools of all patients except one (in the under-12-month age group in 1978) who had a serologic response to rotavirus.

CHNMC, while the remainder are located throughout the Washington metropolitan area. Fifty-four percent of the GHA population is black. The majority of families has an annual income between $10,000 and $25,000.

Patients with complaints of gastroenteritis were seen by the pediatricians of the GHA who provided the outpatient care. Outpatient visits to GHA clinics for diarrhea were recorded on computer records and the information was made available to us, but these illnesses were not studied for viral etiology. Etiologic studies were performed for infants and children enrolled in the GHA who were admitted to the CHNMC for acute gastroenteritis. Criteria for hospitalization were not specifically defined, and the decision to admit was left to the individual pediatrician.

After informed consent had been obtained, stool specimens were collected for detection of viral and bacterial enteric pathogens. Acute and convalescent phase sera were also collected and tested by complement fixation technique for HRV antibody.[6,7] Stool specimens were tested as 2% filtrates or in 2% to 20% suspensions for HRV by electron microscopy (EM), immune electron microscopy (IEM), and rotavirus group enzyme-linked immunosorbent assay.[8-11] Routine bacteriologic testing was performed on stool specimens, in addition to tests for *Campylobacter* sp,[12] *Yersinia* sp,[13] and *Vibrio parahemolyticus*.[14] Assays were also made for heat-labile and heat-stable coliform toxins.[15,16]

RESULTS

Between January 1977 and March 1979, during which time there were three periods of rotavirus prevalence in the community, approximately 29,000 individuals 15 years old or younger were enrolled in the GHA population (Table). The population at risk remained relatively stable during the 27-month period in its total and subgroup profile.

Although the computer-based data on the incidence of gastroenteritis in the GHA outpatient facilities are complete only for calendar years 1977 and 1978, etiologic studies on hospitalized patients are complete through March 1979. Therefore, the estimates for incidence of clinical gastroenteritis are based on a 24-month period, and the estimates for the incidence of hospitalization for HRV infection are based on a 27-month period.

During 1977 and 1978, 1,848 individuals 15 years old or younger were seen in GHA clinics for gastrointestinal illness; the majority of such illnesses occurred in individuals younger than 5 years old. Children 2 years old and younger had 1,011 gastrointestinal illnesses that necessitated a visit to the clinic; this period of observation represented 4,628 person-years. Thus, one of every five individuals at risk in the 24-month-old and younger age group was seen in the clinic for diarrheal disease during 1977 and 1978. During the same 24-month period, 23 GHA patients were hospitalized for gastroenteritis; 19 of them were 2 years old or younger. In this two-year period, approximately one in every 157 infants younger than 1 year old and one in every 485 children in the 1- to 2-year-old age group was hospitalized for gastroenteritis.

From January 1977 through March 1979 (27 months), specimens from 30 of 31 hospitalized GHA patients who were 24 months old and younger were studied microbiologically. Nineteen (63%) of these 30 patients had rotavirus detected in their stools, and one who did not shed rotavirus had a serologic response to rotavirus. The majority of these rotavirus illnesses (12 of 23) requiring hospitalization occurred in individuals younger than 1 year old. Of individuals at risk, one in 272 younger than 1 year old was hospitalized for rotavirus disease (3.7 hospitalized for rotavirus disease per 1,000 at risk per year); the comparable rate for individuals in the 1- to 2-year-old age group was one in 451 (2.2 hospitalized for rotavirus disease per 1,000 at risk per year). Pediatric patients whose specimens were positive for rotavirus and who required hospitalization included 12 black and 11 white patients, a distribution paralleling that of the GHA population. Seven of the white patients and nine of the black patients were male. There were 2.3 times more males than females hospitalized for rotavirus disease. In addition to these younger infants and children, all three children in the 26 to 60-month-old age group and none of four older children hospitalized for gastroenteritis had rotavirus infection.

When hospital admission patterns

for gastroenteritis of any etiology were examined by month, 28 of the 37 (76%) admissions in the study population occurred during January, February, and March.

Other Enteric Pathogens

The specimen from one patient in the 1- to 12-month-old age group yielded a coliform that produced heat-labile enterotoxin. The specimen from one patient 103 months old yielded *Shigella D*. Two patients shed salmonellae, one was in the 1- to 2-year-old age group and the other in the 6- to 15-year-old age group. *Yersinia enterocolitica* was recovered from the stool of one patient, which also yielded rotavirus.

Hospitalization Charges

In 1978 and 1979, the length of hospitalization for 15 of 18 patients with rotavirus disease and from whose records fiscal data were available ranged from one to 13 days, with a mean of 3.8 days. The average charges for hospitalization were $1,530 per patient (minimum, $421; maximum, $4,030).

COMMENT

We have previously reported detection of rotavirus infection in approximately one half of all pediatric patients hospitalized with gastroenteritis.[1] Due to the seasonality of the virus in our area, this percentage increased to 61% during the winter months.[5] In the present study, rotavirus infection was detected in 62% of the 37 pediatric admissions for gastroenteritis studied microbiologically from the population served by GHA in a 27-month period that included three periods when rotavirus infection was prevalent. With the exception of one patient who had dual infection with *Yersinia* organisms and rotavirus, other etiologic agents occurred independently of rotavirus. However, the role of other agents in acute gastroenteritis was minimal; in addition to the *Yersinia* infection cited above, only one patient had a coliform that produced heat-labile enterotoxin, one shed a *Shigella D*, and two patients shed *Salmonella*.

The incidence of hospital admission for rotavirus gastroenteritis in the first two years of life was 2.9 per 1,000 population per epidemic interval. The importance of this virus in gastroenteritis severe enough to necessitate hospital admission decreased precipitously after 2 years of age. From the GHA population, we observed only three patients older than 24 months who had rotavirus in their stools or who demonstrated a significant seroresponse to rotavirus. When examined by calendar month, the proportion of inpatients with gastroenteritis who shed rotavirus was essentially that observed previously during our cross-sectional studies.[1-4] In a previous report, we indicated that patients with gastroenteritis associated with rotavirus were hospitalized for a mean of four days (range, two to 14 days).[5] Thus, the mean (3.8 days) and range (one to 13 days) of hospitalization observed for the GHA patients was comparable to that of the total population served by the CHNMC. This is not surprising, since the GHA population represented a cross-section of the Washington metropolitan area population, and the data derived can thus be applied generally to our urban area.

If the incidence figures are applicable nationwide, the cost of hospitalization for rotavirus gastroenteritis, extrapolated for the United States, would be approximately $27 million per year for the 6,600,000 children less than 24 months old. This estimate may be somewhat high, since it is based on a specialty hospital in the Washington, DC, area. However, the cost of nonhospitalized rotavirus disease (which we are investigating) undoubtedly will extend the monetary impact of rotavirus disease considerably.

Data derived from studying hospitalized patients from this GHA population suggest that at least 50% of admissions for dehydrating gastrointestinal illness are associated with rotavirus. This information, along with outpatient cost data, when it becomes available, should aid in establishing priorities for the need to prevent serious pediatric rotavirus gastroenteritis within the framework of national health care policy.

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Group Health Association, Inc, and Geroge Joseph, MD, cooperated in this study.

References

1. Kapikian AZ, Kim HW, Wyatt RG, et al: Human reovirus-like agent as the major pathogen associated with "winter" gastroenteritis in hospitalized infants and young children. *N Engl J Med* 294:965-972, 1976.

2. Editorial, 1975: Rotaviruses of animal and man. *Lancet* 1:257-259.

3. Middleton PJ, Ssymanski MT, Abbott GD, et al: Orbivirus acute gastroenteritis of infancy. *Lancet* 1:1241-1244, 1974.

4. Brandt CK, Kim HW, Yolken RG, et al: Comparative epidemiology of two rotavirus serotypes and other viral agents associated with pediatric gastroenteritis. *Am J Epidemiol* 110:243-254, 1979.

5. Rodriguez WJ, Kim WH, Arrobio JO, et al: Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children. *J Pediatr* 91:188-193, 1977.

6. Kapikian AZ, Cline WL, Mebus CA et al: New complement-fixation test for the human reovirus-like agent of infantile gastroenteritis, Nebraska calf diarrhea virus used as antigen. *Lancet* 1:1056-1061, 1975.

7. Kapikian AZ, Cline WL, Kim HW, et al: Antigenic relationships among five reovirus-like (RVL) agents by complement fixation (CF) and development of new substitute CF antigens for the human RVL agent of infantile gastroenteritis. *Proc Soc Exp Biol Med* 125:535-539, 1976.

8. Brandt CD, Kim HW, Rodriguez WJ, et al: Gastroenteritis and human reovirus-like agent infection during the 1975-1976 outbreak: An electron microscopic study. *Clin Proc Chila Hosp Natl Med Ctr* 23:21-26, 1977.

9. Kapikian AZ, Kim HW, Wyatt RG, et al: Reovirus-like agent in stools: Association with infantile diarrhea and development of serologic tests. *Science* 185:1049-1053, 1974.

10. Yolken RH, Kim HW, Clem T, et al: Enzyme-linked immunosorbent assay (ELISA) for the detection of human reovirus-like agents of infantile gastroenteritis. *Lancet* 2:263-267, 1977.

11. Yolken R, Wyatt RG, Kapikian AZ: ELISA for rotavirus. *Lancet* 2:819, 1977.

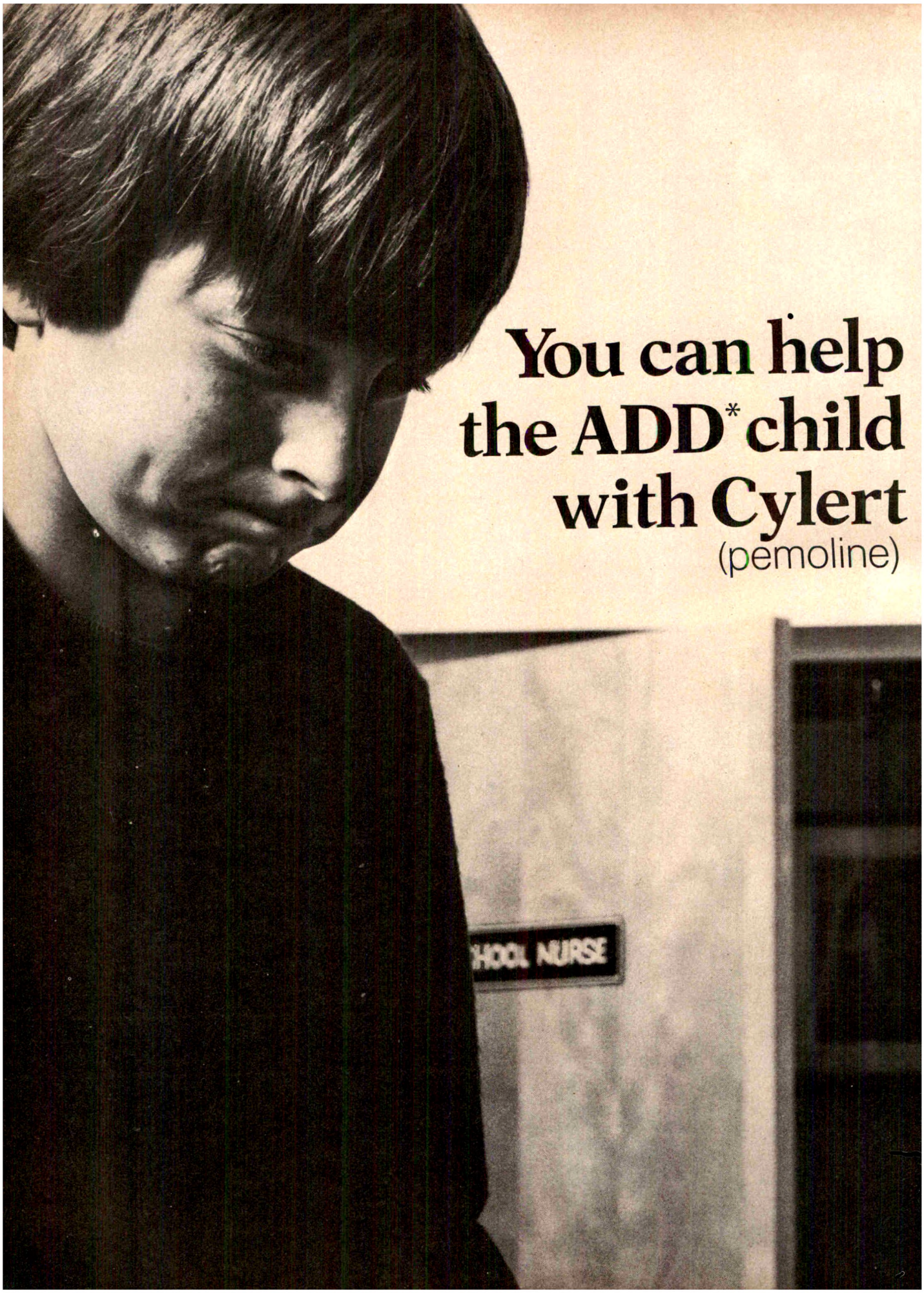
12. Skirrow MB: Campylobacter enteritis: A "new" disease. *Br Med J* 2:9, 1977.

13. Bergstrand CC, Winbrad S: Clinical manifestations of infection with *Yersinia enterocolitica* in children. *Acta Pediatr Scand* 63:875-877, 1974.

14. Zwadyk P: Vibrionaceae, in Joklik WK, Willet HP (eds): *Microbiology*. New York, Appleton-Century-Crofts, 1976, pp 583-592.

15. Sack DA, Sack RB: Test for enterotoxigenic *Escherichia coli* using Y-1 adrenal cells in miniculture. *Infect Immun* 11:334-336, 1975.

16. Dean AG, Chang YC, Williams RG, et al: Test for *Escherichia coli* enterotoxin using infant mice: Application in a study of diarrhea in children in Honolulu. *J Infect Dis* 125:407-411, 1972.



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DESCRIPTION: CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

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CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

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Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD
Contributed by John M. Eckerd, MD, Leroy J. Howard, MD

Figure 1

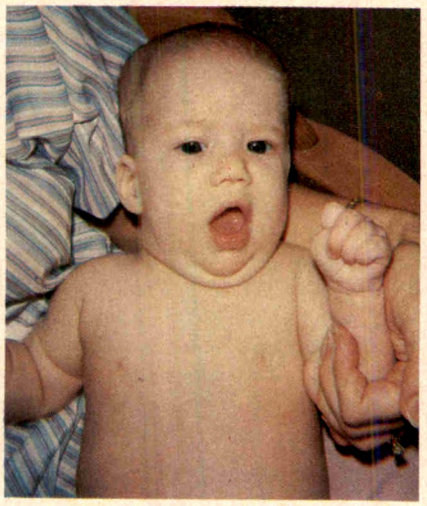

Figure 2

Figure 3

From the Greer (SC) Pediatric Clinic.
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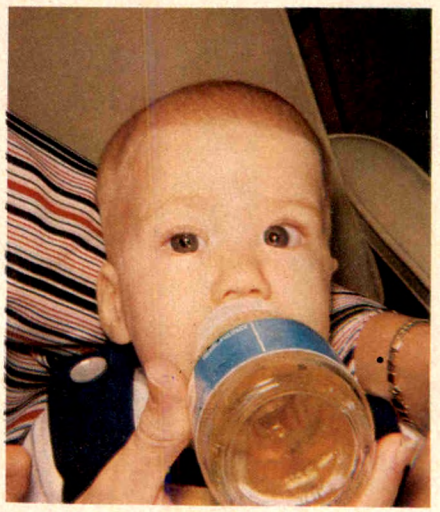

Figure 4

Denouement and Discussion

Marcus Gunn Phenomenon

Fig 1.—Mouth closed and relaxed and eyelid is ptotic.

Fig 2.—Mouth opened and right eyelid is raised.

Fig 3.—Jaw is relaxed during sucking.

Fig 4.—Infant is sucking and eyelid is raised.

Manifestations

Marcus Gunn phenomenon consists of unilateral ptosis at rest with elevation of the eyelid when the mouth is open. This condition is classified under the general heading of "synkinetic ptosis," and the most common type is trigemino-oculomotor synkinesis, or the jaw-winking phenomenon. It is most noticeable during infancy, at which time rapid up and down movements of the eyelid are apparent when the infant is nursing. If the jaw is deviated to the affected side, the ptosis increases but if it is deviated to the unaffected side or if the jaw is projected forward, elevation of the eyelid occurs. It is usually present on the left side and is almost always unilateral. Although there are various theories concerning the etiology of this phenomenon, most believe that during embryogenesis the fifth cranial nerve (trigeminal) fibers were misdirected into the third cranial nerve (oculomotor). As a result of this, when the mouth is open, or sucking takes place, nerve impulses are sent to the external pterygoid muscle which activates the levator palpebral superioris muscles on the same side via the third nerve, causing the eyelid to elevate.

Genetics

It is usually sporadic, although it has been reported inherited in an irregular autosomal dominant manner.

Treatment

Some of the patients have spontaneous improvement with age. Surgical treatment consists of bilateral levator tenotomy and suspension of both eyelids from the brows with a fascia lata sling. In more severe cases the cosmetic results of the surgical resection are not cosmetically better than the original condition.

References

1. Kuder GG, Laws HW: Hereditary Marcus Gunn phenomenon. *Can J Ophthalmol* 3:97-98, 1968.
2. Duke-Elder S: *System of Ophthalmology: Vol III, Normal and Abnormal Development.* St Louis, CV Mosby Co, 1974, vol 3, part W, pp 902-903.
3. Walsh FB, Hoyt FW: *Clinical Neuro-Ophthalmology.* Baltimore, Williams & Wilkins Co, 1969, vol 1, p 312.
4. Beard C: *Ptosis.* St Louis, CV Mosby Co, 1976.

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Review

Hypernatremic Dehydration of Infancy

An Epidemiologic Review

Nigel Paneth, MD, MPH

Hypernatremic dehydration (HD) is dehydration associated with an elevated serum sodium concentration that is generally defined as a level of 150 mEq/L or higher. Hypernatremia is seen in a variety of clinical states in infancy, but this article is concerned with its occurrence in the clinical setting of diarrheal dehydration in otherwise healthy infants. Such a focus is a practical one, as this is the setting for well over 90% of the cases of HD in infants younger than 2 years of age. Diabetes insipidus, renal disease, mental deficiency, and a number of other conditions may predispose to HD, but although they may help elucidate pathophysiologic findings, they are relatively unimportant contributors to the overall incidence of the disorder.

CLINICAL FEATURES

The clinical importance of HD stems from its noticeable distinction from nonhypernatremic dehydration (NHD) as a clinical problem. Almost all clinical reports comment on its relatively high mortality (Table 1). Infants with HD usually have a very different clinical appearance from infants with NHD. They have fewer of the familiar signs of dehydration, such as weak pulses and poor capillary perfusion, and more signs of CNS dysfunction—irritability, lethargy or even coma, and convulsions. A number of observers have noted a peculiar "doughy" feeling to their skin. These differences have been explained by the fact that sodium is essentially an extracellular ion and so tends to draw water into the interstitial and intravascular space, thus maintaining intravascular volume at the expense of cellular desiccation, including desiccation of the cells of the brain and the skin. As the brain is enclosed within a fixed size container, its shrinkage causes vascular damage, capillary and venous congestion, subarachnoid and parenchymal hemorrhages, and thrombosis of venous sinuses. These abnormalities and occasionally subdural hematomas as well have been found frequently in autopsied cases.[1,9-11] This pathophysiologic sequence has been well documented in animals in which the disorder has been experimentally reproduced.[12,13] Parallel to these findings are the elevated CSF protein and xanthochromia commonly found in HD.[1,14,15] The risk of CNS signs increases with the serum sodium concentration and has been reported to be as high as 70% in infants with serum sodium concentrations greater than 158 mEq/L.[7] It is apparent that the rate of development of hypernatremia plays an important role in the degree of CNS dysfunction.

Treatment of HD is difficult as the clinician must tread a fine line between correcting the hypernatremic state and inducing further CNS signs, especially convulsions, by overly rapid water administration. Convulsions are in fact common during therapy,[3,5,16] and autopsied cases that have received intravenous therapy have often shown cerebral edema in the presence of severe dehydration.[5,14,16]

Even if the infant with HD survives both disease and therapy, it is by no means certain that he or she will be left without a residual handicap. Infants with severe brain damage after HD have been described by several authors.[3,11,17,18] Two systematic attempts to trace and examine survivors have been reported in the literature.[5,18] The rates of persistent neurologic abnormality found have been 11% and 15%, consisting of intellectual deficits, seizure disorders, and spastic plegias. It should be noted that in neither study were patients with NHD followed up, nor could the authors give assurance that their patients with HD were free of brain damage prior to their illness. In a common disorder, even a small eleva-

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tion in the risk of neurologic or intellectual deficit cannot be ignored, and the claim has been made that, "1,000 children of school age may have an educational or social handicap attributable to hypernatremia" in the United Kingdom.[19]

The high mortality and brain-damaging effects of HD clearly make it a disease worth preventing. But this assertion raises important questions as to the nature of HD. To what extent is it a separate entity from NHD? Is it simply one tail of the distribution of diarrheal dehydration, that associated with a high serum sodium concentration? Is it perhaps a particularly severe form of dehydration, the expected outcome for all infantile dehydration if allowed to progress long enough? Is it a disease caused by a separate agent? Is it the response of certain hosts to infection with the same causative agent associated with NHD? Before attempting to frame an epidemiologic answer to these questions, it will be useful to review the pathogenetic mechanisms likely to be operative in the production of HD.

PATHOGENESIS

Infants, because of certain physiologic characteristics, are predisposed to becoming dehydrated. They have a much larger surface area in relation to height or weight than do adults, and consequently have relatively larger evaporative water losses. Although it is not clear exactly at what age infants are able to fully concentrate urine, some normal infants are unable to concentrate beyond 700 mOsm/L in the early months of life.[20-22] Thus, infants would be expected to require larger amounts of water to excrete a given renal solute load. These two factors are probably the primary reason for the fact that a 4-kg infant has a daily water turnover 20% that of a 70-kg adult, despite weighing only 6% as much.[23] Thus, limitation of access to fluids or excessive losses of fluid of any sort would be expected to lead to dehydration much more rapidly in an infant than in an adult. It should be noted that these factors all deal with the infant's relation to water, so that one might ask why hypernatremia does not occur in all dehydrated infants. Nonetheless, in all parts of the world, the largest proportion of dehydrated infants have serum sodium levels within the normal range. Presumably, enteric losses of salt and water are kept in balance by the combination of oral intake and physiologic adjustments.

Table 1.—Mortality in Hypernatremic Dehydration in Several Studies

Source, yr	No. of Deaths/Cases	Mortality, %
Finberg and Harrison,[1] 1955	8/69	11
Colle et al,[2] 1958	4/17	23.5
DeYoung and Diamond,[3] 1960	2/10	20
Macaulay and Blackhall,[4] 1961	3/30	10
Morris-Jones et al,[5] 1967	10/50	20
Ironside et al,[6] 1970	2/47	4
Rosenbloom and Sills,[7] 1975	4/14	28
Rosenfeld et al,[8] 1977	2/67	3
Total Series Combined	**35/304**	11.5

Table 2 gives some of the factors that might predispose an infant to hypernatremia, given diarrheal dehydration. Included in Table 2 are the known disease states that predispose to HD and their mechanism of action. Some of these mechanisms are age dependent in a roughly linear fashion. For example, the infant's relative lack of renal concentrating ability is more pronounced in the newborn period and especially so in premature infants. It is also apparent that these mechanisms may very well act in concert. A very young infant will not be able to handle the dietary renal solute load appropriate for an older infant, and particularly so if he or she is febrile.

It can be seen that the determinants of hypernatremia in a dehydrated infant are quite well understood. The distribution of these determinants is, however, poorly documented, and so the relative importance of any one of these mechanisms in producing HD in the population of infants cannot be weighed against any other.

EPIDEMIOLOGY OF NONSPECIFIC DIARRHEAL DISEASE OF INFANCY

As noted earlier, almost all cases of HD in infants are produced by diarrheal disease. Thus, the epidemiology of HD reflects to some extent the epidemiology of this underlying cause, and some sense of the occurrence and distribution of infantile diarrheal disease is necessary to place HD in its proper perspective.

In many parts of the world, diarrheal disease is the single largest contributor to infant mortality and causes a formidable number of deaths. Diarrheal disease caused 645 infant deaths in the United States in 1977, a toll exceeded only by pneumonia among infectious causes in the postneonatal period,[34] The age of highest risk in the developing world seems to be the weaning period when infants are exposed for the first time to a multitude of infectious agents capable of causing toxic enteric manifestations. At this time, attack rates may reach 275/100 children per year, and mortality 50/1,000 children per year.[35] As might be expected, attack rates vary with the degree of sanitation in the community, and mortality varies in relation to this factor, nutritional status, and possibly access to medical care.

No specific pathogen can be isolated from the majority of infants with diarrhea. In areas where known enteric pathogens such as *Salmonella*, *Shigella*, and parasites are endemic, the isolation of these in cases of infantile gastroenteritis rarely reaches 40%.[35] Nevertheless, epidemiologic evidence incriminates an infectious agent in almost all cases. Spread within families and institutions is notoriously common, and a definite incubation period is usually found. It is also well known that a multitude of agents not considered classic enteric pathogens can cause gastroenteritis. Adenoviruses and several strains of echovirus

Table 2.—Mechanisms by Which Hypernatremia May Be Produced in Diarrheal Dehydration

Inability to Gain Access to Water
Immaturity
Brain damage
Hypothalamic thirst center damage
Anorexia
Excess Renal Solute Load
Error in preparation
Solute load inappropriate for age of child
Solute load inappropriate for nature of losses
Excess Pure Water Loss
Agent producing very hypotonic stools
Fever
Hyperventilation
Elevated ambient temperature
Decreased Renal Concentrating Ability
Immaturity
Renal unresponsiveness to antidiuretic hormone
Lack of antidiuretic hormone

have been known to cause localized outbreaks among infants.[36-39]

In recent years, attempts to isolate specific agents in infantile diarrhea have been more productive. Two agents, each with properties making its identification difficult, have been implicated. Toxigenic strains of *Escherichia coli* have been found increasingly often in the stools of patients with diarrhea as the technique for identifying *E coli* exterotoxin has become more prevalently used. A considerable proportion of traveler's diarrhea is now thought to be of this origin.[40,41] In infants, studies have occasionally implicated this agent.[28,42,43]

The "reovirus-like agent" has also been implicated in many cases of diarrhea in infants.[44-47] This circularly shaped virus, also referred to as rotavirus or orbivirus, has been identified so far only by electron microscopy and has not yet been grown successfully in the laboratory. The evidence that this may be the single agent most responsible for infantile diarrhea is beginning to accumulate.[48-51]

EPIDEMIOLOGIC FEATURES OF HYPERNATREMIC DEHYDRATION

Sources and Limitations of Data

As diarrheal disease is not reportable to government sources, what little epidemiologic knowledge we have about HD must be based on the series of cases described in the literature.

Table 3.—Proportion of Infants Hospitalized for Dehydration With Hypernatremia*

Source, yr	Location of Study	% With Hypernatremia
United States		
Tarail et al,[24] 1953	Pittsburgh	11
Finberg and Harrison,[1] 1955	Baltimore	25
Weil and Wallace,[17] 1956	Cleveland	20
Skinner and Moll,[16] 1956	Seattle	23
Colle et al,[2] 1958	Minneapolis	68
Franz and Segar,[25] 1959	Indianapolis	9
Darrow and Welsh,[26] 1960	Kansas City, Mo	11
DeYoung and Diamond,[3] 1960	Chicago	21
Bruck,[27] 1969	Buffalo	34
Rosenfeld et al,[8] 1977	New York	23
United Kingdom		
Macaulay and Blackhall,[4] 1961	Manchester	30
Jacobs et al,[28] 1970	Manchester	19
Ironside et al,[6] 1970	Manchester	63
Chambers and Steel,[29] 1975	Leeds	60
Developing nations		
Ahmed and Webb,[30] 1963	India	1.5
Ahmed and Agusto-Odutola,[14] 1970	Nigeria	20
Prinsloo and Kruger,[31] 1970	South Africa	1.5†
Beatty et al,[32] 1974	South Africa	4
Kassel et al,[33] 1974	South Africa	8†

*Serum sodium level greater than 150 mEq/L.
†Serum sodium level greater than 145 mEq/L.

Table 4.—Composition of Diarrheal Stools*

Intake	No. of Periods	Na, mM/L of H_2O	K, mM/L of H_2O	Cl, mM/L of H_2O	H_2O Content, %	Osmolality, mOsm/kg of H_2O
Milk mixture	10	41	60	27	93	...
Milk mixture	14	59	27	51	97	...
	80†	65	45	51	...	...
Milk mixture	13	30	52	38	...	...
Milk mixture	2	35	18	36	...	...
Electrolyte mixture	10	57	35	20	95	313
Intravenous (IV) fluids only	7	64	44	55	95	...
IV fluids only	6	46	49	26	...	...
Weighted average	...	58	44	45	96	...

*From Koch et al.[23]
†Periods during which entire stool was collected ranged from two to five days, with exception of the study of Finberg et al,[88] where data represents single aliquots of stool collected at time of admission from infants with diarrhea.

Some of these series are reports of infants with HD and their characteristics; others report series of cases of diarrheal dehydration and contrast the characteristics of HD with NHD. The latter category of study is more useful and unfortunately rarer. A list of several studies of both kinds can be found in Table 3.

Some caveats apply to the interpretation of data reported in all of the studies. First, different categories of infants are included under the term HD. Although a cutoff point of 150 mEq/L is used rather uniformly, some studies describe all infants in whom such a value was found, others describe only infants with diarrheal dehydration as a predisposing cause.

Second, all reported series consist of

hospitalized cases only. It is possible that an infant may die before arriving at the hospital and that his death may be attributed to other causes.[52] It is unlikely, however, that clinically important cases otherwise escape medical attention, at least in the developed world. The most important problem is that different criteria for hospitalization and drawing of electrolytes operate in different series.

Third, HD is generally reported as a percentage of dehydrated infants. Thus, it is a conditional probability with the denominator population being all dehydrated infants hospitalized. From these data, we can make no definite inferences as to the true incidence of HD. Nevertheless, this conditional probability is of great interest in itself, as it tells the risk of HD developing given the stress of diarrheal dehydration.

Environmental Attributes of HD

Geography.—An important conclusion to be drawn from the data in Table 3 is that the proportion of dehydrated infants found to be hypernatremic is much higher in North America and Great Britain than in the less developed countries of Africa and Asia. The report from Nigeria is an exception, but it is worth noting that it comes from an urbanized community—Lagos. Within the United States, there seem to be some areas with higher incidences than others, but the numbers of cases reported, for example in the Minneapolis study, preclude any firm conclusions. The possible explanations for this variation are many, and will be considered under the appropriate categories.

Infecting Agent.—There is little evidence that there are differences in the agents likely to be isolated from HD and NHD. Certain of the bacterial pathogens may, however, be associated with a tendency to NHD. Cholera, for example, produces a loss of essentially isotonic fluid in large volume and, thus, usually produces either isonatremia or hyponatremia. There is some evidence that enteropathogenic *E coli* may also be more likely to be associated with NHD as the stool electrolyte level tends to be somewhat higher in this disease than in nonspecific diarrhea.[53] Jacobs and Holzel,[5] in reporting a hospital outbreak of gastroenteritis caused by *E coli* serotype 0114, noted that the incidence of HD was much lower (0/21) in the affected infants than in infants admitted for diarrheal dehydration during the same period of time (9/16). Attribution of these differences to the difference in isolated agents is limited by the fact that the infants affected by *E coli* in this study had all been hospitalized, many with chronic illness and some of them malnourished. The affected infants also had a greater incidence of vomiting, although the effect of vomiting on serum sodium concentrations is variable.

An agent may be more likely to cause HD for reasons other than its effect on the composition of gastroenteric losses. Organisms producing fever and hyperpnea might be expected to be associated with a greater tendency with hypernatremia because of the increased water losses. To my knowledge, however, no series has been reported in which a comparable group of infants with HD and NHD have been shown to have any differences in the likelihood of having any specific organism isolated from them nor even in the likelihood of having an organism isolated at all. Early studies of infants with diarrhea in which the techniques necessary for the identification of reovirus-like agents and *E coli* enterotoxin were used did not commonly report on serum sodium levels in affected or unaffected infants.[42,44,46,47] More recent studies describing the clinical picture in diarrheal disease caused by the reovirus-like agent do not report any particular predisposition to hypernatremia.[48-51] Only one of 27 infants from Toronto studied by Tallett et al[51] had a serum sodium concentration greater than 150 mEq/L. In the series by Rodriguez et al,[49] 5% of the infants with reovirus diarrhea were hypertonic, whereas 16% of the infants with diarrhea from whom reovirus was not isolated were hypertonic, a difference that is statistically significant. In this study, infants infected with reovirus were somewhat younger, which might explain a greater propensity to electrolyte disturbance.

Feeding History and Nutritional Status.—Nutritional and dietary differences between the developing and underdeveloped world seem likely candidates for variables capable of explaining the difference in relative incidence of HD. It has been known for some time that malnourished infants are predisposed in general to hypoelectrolytemia, and much work has been done in attempting to elucidate the biochemical derangements in malnutrition.[23,54-58] In the underdeveloped world, a large proportion of infants with NHD have hyponatremia even without the isolation of organisms likely to cause considerable sodium losses.

If undernutrition predisposes to hyponatremia, does overnutrition in some sense predispose to hypernatremia? As noted earlier, a pathogenetic mechanism does exist by which the protein and electrolyte content of an infant's diet, its renal solute load, might, if present in excess, cause renal losses of water that could predispose to HD. There is also ample evidence that both protein and sodium are present in the diet of US infants in rather large amounts. The survey by Filer and Martinez[59] of 4,000 representative 6-month-old infants found that the mean protein intake in grams per 1,000 calories of intake was more than twice the National Research Council's recommended allowance. This report also noted that although caloric intakes for South Korean infants were from 74% to 85% of those of US infants, protein intakes were only 32% to 43% of those of US infants. Sufficient publicity has been given to the salt content of infant foods so as not to require a comprehensive review here. Suffice it to say that mean sodium intakes in infants in the United States increase at a greater rate than weight or caloric intake during the first year of life, and at one time averaged about 6 mEq/kg/day, or about five times what would be provided in a breast-milk diet.[60,61] It is likely that recent changes in infant food salt content have reduced these figures. Although some of the excess protein and sodium in US infant diets is undoubtedly incorporated into the greater body

mass of US infants, much of it must be excreted in the urine, drawing water with it.

Do infants with HD have a different dietary history from infants with NHD? Although this would seem a logical question to ask, surprisingly little attention has been given to the dietary patterns of dehydrated infants. Some reported series of cases have presented data on the intake of the infant just prior to admission. Franz and Segar[25] showed that in their series infants with HD were more likely to have been treated with a powdered oral electrolyte solution (Lytren), which has a sodium concentration of 50 mEq/L when properly constituted. This association was also noted by Colle and Ayoub.[2] After these reports and an editorial by Finberg,[62] the electrolyte solution was adjusted to provide a sodium concentration of 25 mEq/L when reconstituted. A number of other studies, however, failed to show an association between HD and excessive salt intake prior to admission.[4,63] Berenberg et al[64] have shown that boiled skim milk, once commonly recommended for infants with diarrhea, may also predispose to hypernatremia. Thus, it seems clear that the nature of an infant's intake during his illness can influence his chances of becoming hypernatremic, although the evidence is slim that excess solute in the fluids prescribed for infants with gastroenteritis is now a highly prevalent causative factor in the United States.

That the diet generally fed to infants can produce hypernatremia is well known from the large number of cases of HD reported to have been caused by errors in formula preparation.[10,65-70] Outbreaks of hypernatremia in neonates associated with improper formula constitution have been reported from France and Spain.[71,72] Gross errors in formula preparation are easily recognized by history, but several British authors have suggested that smaller errors in formula preparation, such as using heaped rather than level teaspoons of dried formula, are much commoner than suspected.[67,73,74] These errors are almost always on the side of overconcentration rather than overdilution. Clearly, such errors are much more likely to occur when powdered formulas are used, and the fact that powdered formulas constitute less than 10% of the formula market in the United States[75] limits the application of this factor as a determinant of HD on this side of the Atlantic.

The question of whether diets not generally recognized to be harmful may place a dangerous load on the infant's kidneys has been raised by a number of investigators. The renal solute level of commonly used humanized milks is almost twice as high as that of breast milk, and that of cow's milk is three times as high.[76] Two studies in Great Britain have shown that a random urine osmolality is likely to be higher in a healthy breast-fed infant.[67,77] One of these studies[77] also showed that serum osmolality was higher in formula-fed infants than in breast-fed infants, and that it was higher still in infants of the same age who were receiving both formula and solid foods. Another British study was unable to reproduce these findings in serum osmolality, but did note a substantial difference in BUN levels, with formula-fed infants having higher levels than breast-fed infants.[78] To my knowledge, there is only one published report of HD occurring in an otherwise healthy exclusively breast-fed infant.[79]

These data are provocative but thus far the link between these findings and HD has not convincingly been made. Only one attempt to obtain data on the diets generally fed to infants with HD and with NHD has been made. Chambers and Steel[29] found a statistically significant correlation between the sodium concentration and the total osmolarity of the formulas generally fed to infants and their risk of having HD. Generalization from this study is, however, limited by the fact that the infants involved had an unusual age distribution for diarrheal dehydration, the mean age for the infants with HD being 2.2 months and that for infants with NHD being 1.8 months. The study period in this report was February to September, not the peak season for diarrheal dehydration in the United Kingdom, and thus the study might have selected atypical cases.

Temporal Variation.—No definite secular trend in the incidence of HD can be identified although it has been suggested that the disorder is more common than in the past. Some British authors have suggested that the incidence is now beginning to decline in Great Britain and have linked this decline to the greater use of humanized milks.[80-82] Given the ever-changing criteria for admission to hospital and determination of electrolytes, it is not possible to make any definite statements about such trends from the published literature.

There is a definite seasonal variation in infantile diarrhea, with the colder months being modal in the developed world. This in itself is interesting as in the past, summer was the season for diarrhea the world over. Both *Salmonella* and the enteroviruses have a predilection for the summer months, and it is possible that in the past, with poor sanitation, these organisms may have been important causes of diarrhea.

Data conflict on the question of whether HD and NHD have a different seasonal variation, but the weight of the evidence seems to be on the side of a winter-time peak for both disorders, which is more pronounced for HD, at least in the United States. Bruck[27] analyzed the monthly breakdown of serum sodium levels in dehydrated infants during a 13-year-period in Buffalo, NY, and found a statistically significant difference in the proportional incidence of HD in winter as opposed to summer, with a higher percentage of dehydrated infants found to be hypernatremic in the winter months. The proportion of HD in each winter month varied little, ranging from 36% to 49% of all dehydrated infants. Since the number of admissions in the winter months was four times as high as those in summer months, the peak incidence for both forms of dehydration was in the winter. Rosenfeld et al[8] found HD in 63% of the infants with diarrhea hospitalized for diarrhea in December, January, and February in contrast to a 23% proportion over the entire three-year period examined in their study. In contrast to this experience is the

aforementioned study by Chambers and Steel[29] who found a 60% rate of HD in the period February to September. Macaulay and Blackhall[4] were unable to find any differences in seasonal occurrence between patients with HD and NHD in their study. Winter seems to be the peak period for reovirus infection,[47,51] and it is thus tempting to consider a possible link between HD and this organism, but, as noted, reports published thus far do not support such an association.

Host Characteristics in HD

Most series do not report noticeable age differences in patients with HD and NHD, and two authors specifically note that the mean age of patients was the same.[1,4] In eight series in which the mean age of patients with HD was given, it ranged from 6 to 9 months in seven of them, and was 2.2 months in one series from Great Britain. Thus, in most instances it seems that HD occurs in infants who are in the same age range as most infants with diarrheal dehydration, although occasionally younger infants may be involved, particularly if formula errors are operative.

No consistent trends have been noted in any studies in race or ethnicity of patients with HD, and socioeconomic features have rarely been examined. Geographic variation cannot be explained by different racial susceptibility as most US series contain a substantial proportion of both black and white infants.

Many studies of HD have noted a greater tendency for such infants to be febrile. In one study,[4] this difference was statistically significant. One might conclude that a virus causing fever as well as diarrhea would be more likely to cause HD. On the other hand, it should be remembered that hypernatremia itself may cause fever. Victims of the epidemic of salt poisoning in Binghamton, NY, were uniformly febrile although the cause was clearly noninfectious.[9] High-protein feeds given to premature infants have been associated with fever and lethargy.[63] This phenomenon has been termed protein fever and is thought to be mediated by hyperosmolarity (H. H. Gordon, MD, oral communication, Jan 14, 1977).

Respiratory rate has not often been contrasted in infants with HD and NHD but has occasionally been found to be higher in infants with HD. Much the same argument applies as with fever, as rapid grunting respirations were a hallmark of salt-poisoned infants.[9]

Is it possible that infants with HD are simply the most severely dehydrated? There is some evidence that in series of dehydrated infants there is a tendency for the hypernatremic infants to be more severely affected. Application of clinical criteria to the assessment of dehydration would be expected to produce a bias in favor of declaring infants with NHD the most dehydrated for the reasons outlined in the first part of this article. This trend was found in the series by Macaulay and Blackhall[4] who noted that infants with HD were more likely to be classified as having mild dehydration than infants with NHD. Ironside et al,[6] on the other hand, found that 89% of their infants with HD were classified as moderate or severe in degree of dehydration, as compared with 61% of the infants with NHD. In the series by Colle and Ayoub,[2] mean BUN levels were higher in the group with HD. However, BUN levels may not be purely indicative of dehydration in this disorder, as hypernatremia has a well-established nephrotoxic effect.[84] An interesting set of data is available from a recent publication on CSF osmolarity in HD by Habel and Simpson.[85] This article records serum sodium concentration, BUN level, and the volume of fluid deficit of dehydrated infants, the latter calculated by comparing infants' weights on admission with their weights when rehydrated. The data show a slight tendency for the most severely hypernatremic infants to be the most dehydrated, but the relationship is far from linear. By way of contrast, Rodriguez et al[49] found that reovirus diarrhea was both more likely to cause dehydration and less likely to cause hypernatremia than nonreovirus diarrhea. Although infants with HD are probably on the whole somewhat more dehydrated than infants without HD, the data of Habel and Simpson show that severe dehydration is not a prerequisite for hypernatremia since 50% of this series of infants with HD were less than 10% dehydrated.

Classic teaching is that the tonicity of the body fluids in diarrheal dehydration relates directly to the tonicity of the losses in the stool and/or vomitus. Thus, stool electrolyte values might be expected to differ in HD and NHD. As noted earlier, however, other factors would be expected to enter into the equation, especially in small infants. In cholera, it has been known since at least 1832 that there is a direct relationship between stool and serum sodium.[86] It has even been shown that in pediatric cholera, stool sodium concentration is lower than in adult cholera and, as a consequence, that serum sodium levels are somewhat higher than in adults.[87] It comes somewhat as a surprise then to discover that for nonspecific diarrhea of infancy no such relationship can be documented. Finberg et al[88] have shown that over a range of sodium concentration in the serum from 118 to 170 mEq/L no relationship was found to the stool sodium concentration in dehydrated infants. This lack of a relationship was also found by Bruck et al[39] in a smaller series. Table 6, from Kooh and Metcoff,[23] shows that in several studies from different parts of the United States, performed on infants on different diets, stool sodium concentration in diarrhea tended to be remarkably similar. The only study that reports on stool sodium concentration in reovirus diarrhea[51] found it to be slightly lower than the figure given in the review by Kooh and Metcoff. The fact that the infants in this study were not particularly predisposed to HD supports the conclusion that the variance in serum sodium concentration in diarrheal disease is not generally mediated through the stool sodium concentration.

Some other observations have sporadically been made about infants with HD and have been speculated to be causative. A few authors have noted that infants with HD are more likely to have an explosive onset of their disease. Of course, cholera has

the most explosive onset of any infectious diarrhea, but does not produce hypernatremia. Nevertheless, the principle involved may be that in diarrheas of rapid onset serum sodium concentrations may reflect stool losses more closely. If infant diarrhea is by and large hypotonic as noted in Table 6 by Kooh and Metcoff,[23] this may indeed be an explanatory variable. Unfortunately, carefully controlled comparative data on this variable have not generally been obtained.

Noting the high incidence of the disorder in the winter months, some authors have speculated that low-humidity heating systems may be a factor.[8] No actual observations have been made to confirm or deny this.

CONCLUSIONS AND DIRECTIONS FOR FUTURE STUDY

Hypernatremic dehydration is almost certainly a multifactorial disease that can be produced by a variety of pathways or combinations of pathways. From the limited epidemiologic information available only rather tentative conclusions can be drawn. It seems unlikely that the source of variance in serum sodium concentration in dehydration is due to differences in the infecting agent. The fact that both HD and NHD have peak incidences in the same age group at the same time of year suggests that a single agent is operative and that the differences in sodium concentrations among infants relates to a difference in host response. This difference may be the particular form the illness takes in some infants as opposed to others, the manner in which it is dealt with, or some underlying difference in the host himself or herself. A strong line of evidence implicates dietary factors as possibly producing a host that is unusually susceptible to HD, but definite links between these two variables have not been established.

Future research efforts should be directed at the elucidation of the relationship between HD and dietary experience, as well as between HD and any of the more recently discovered enteric pathogens. It would be of especial interest to know more about the patterns of electrolyte disturbance in infants from whom the reovirus-like agent is isolated. Such studies should be based on information prospectively collected from infants with both HD and NHD selected in as random a fashion as possible. Clinical and demographic data should be obtained on both groups of infants so as to ascertain their comparability and to stratify data along lines that seem appropriate, eg, degree of dehydration, etc. If the dietary experience is an important causal variable in the production of HD, it is a variable possibly amenable to modification. Thus, searching for this association has the practical importance of possibly leading to a means of preventing this disorder and thereby causing a small, but not necessarily trivial, reduction in the prevalence of childhood handicap.

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References

1. Finberg L, Harrison HE: Hypernatremia in infants: An evaluation of the clinical and biochemical findings accompanying this state. *Pediatrics* 16:1-14, 1955.

2. Colle E, Ayoub E, Raile R: Hypertonic dehydration (hypernatremia): The role of feedings high in solutes. *Pediatrics* 22:5-12, 1958.

3. DeYoung VR, Diamond EF: Possibility of iatrogenic factors responsible for hypernatremia in dehydrated infants. *JAMA* 173:1806-1808, 1960.

4. Macaulay D, Blackhall MI: Hypernatremic dehydration in infantile gastroenteritis. *Arch Dis Child* 36:543, 1961.

5. Morris-Jones PH, Houston IB, Evans RC: Prognosis of the neurological complications of acute hypernatraemia. *Lancet* 2:1385-1389, 1967.

6. Ironside AG, Tuxford AF, Heyworth B: A survey of infantile gastroenteritis. *Br Med J* 3:20-24, 1970.

7. Rosenbloom L, Sills JA: Hypernatraemic dehydration and infant mortality. *Arch Dis Child* 50:750, 1975.

8. Rosenfeld W, deRomana GL, Kleinman R, et al: Improving the clinical management of hypernatremic dehydration. *Clin Pediatr* 16:411-417, 1977.

9. Finberg L, Kiley J, Luttrell CN: Mass accidental salt poisoning in infancy: A study of a hospital disaster. *JAMA* 184:187-190, 1963.

10. Anderson WR, Quie PG: Cyanosis, seizures, and hypernatraemia in a 2-week-old infant. *Minn Med* 51:97-103, 1968.

11. Finberg L: Pathogenesis of lesions in the nervous system in hypernatremic states: I. Clinical observations of infants. *Pediatrics* 23:40-45, 1959.

12. Finberg L, Luttrell C, Redd H: Pathogenesis of lesions in the nervous system in hypernatremic states: II. Experimental studies of gross anatomic changes and alterations in the chemical composition of the tissues. *Pediatrics* 23:46-53, 1959.

13. Sotos JF, Dodge PR, Meara P, et al: Studies in experimental hypertonicity: I. Pathogenesis of the clinical syndrome, biochemical abnormalities and cause of death. *Pediatrics* 26:925-938, 1960.

14. Ahmed I, Agusto-Odutola TB: Hypernatraemia in diarrhoeal infants in Lagos. *Arch Dis Child* 45:97-103, 1970.

15. Shaywitz BA: Extreme elevations of cerebrospinal fluid protein: Association with hypernatremic dehydration. *Am J Dis Child* 120:84-87, 1970.

16. Skinner AL, Moll FC: Hypernatraemia accompanying infant diarrhea. *Am J Dis Child* 92:562-575, 1956.

17. Weil WB, Wallace WM: Hypertonic dehydration in infancy. *Pediatrics* 17:171-183, 1956.

18. Macaulay D, Watson M: Hypernatraemia in infants as a cause of brain damage. *Arch Dis Child* 42:485-491, 1967.

19. Chambers TL: Hypernatraemia: A preventable cause of acquired brain damage. *Dev Med Child Neurol* 17:91-94, 1975.

20. Polacek E, Vocel J, Neugebauerova L, et al: The osmotic concentrating ability in healthy infants and children. *Arch Dis Child* 40:291-295, 1965.

21. Winberg J: Determination of renal concentration capacity in infants and children without renal disease. *Acta Paediatr* 48:318-328, 1959.

22. Edelmann CM, Barnett HL, Troupkou V: Renal concentrating mechanisms in newborn infants: Effect of dietary protein and water content, role of urea, and responsiveness to antidiuretic hormone. *J Clin Invest* 39:1062-1069, 1960.

23. Kooh SW, Metcoff J: Physiologic considerations in fluid and electrolyte therapy with particular reference to diarrheal dehydration in children. *J Pediatr* 62:107-131, 1963.

24. Tarail R, Bass LW, Runco AS: The frequency and nature of hypertonicity of the body fluids in infantile diarrhea. *Am J Dis Child* 86:658, 1953.

25. Franz MN, Segar WE: The association of various factors and hypernatremic diarrheal dehydration. *Am J Dis Child* 97:298-302, 1959.

26. Darrow DC, Welsh JS: Recent experience in the treatment of diarrhea in infants. *J Pediatr* 56:204-210, 1960.

27. Bruck E: Seasonal incidence of hypertonic dehydration in diarrhea of infants: Experience in Buffalo from 1954 to 1967. *Am J Dis Child* 118:582-584, 1969.

28. Jacobs SI, Holzel A, Wolman B, et al: Outbreak of infantile gastroenteritis caused by *Escherichia coli* 0114. *Arch Dis Child* 45:656-663, 1970.

29. Chambers TL, Steel AE: Concentrated milk feeds and their relation to hypernatraemic hydration in infants. *Arch Dis Child* 50:610-615, 1975.

30. Ahmed I, Webb JK: Childhood diarrhea in S. India with particular reference to fluid and electrolyte disturbance. *Indian J Child Health* 12:85-91, 1963.

31. Prinsloo JG, Kruger H: Electrolyte and nutrition status of Bantu children with gastroenteritis. *S Afr Med J* 44:491-493, 1970.

32. Beatty DW, Mann MD, Heese H, et al: Acute dehydrating gastro-enteritis in undernourished infants. *S Afr Med J* 48:1563-1568, 1974.

33. Kassel HR, Buchanan N, Moosa GM: The treatment of the dehydrated Bantu child. *S Afr Med J* 44:1203-1206, 1970.

34. *Monthly Vital Statistics Report: Final Mortality Statistics, 1977.* National Center for Health Statistics, US Dept of Health, Education, and Welfare Publication No. (PHS)79-1120, vol 28, No. 1, suppl, May 11, 1979, p 21.

35. Benenson AS (ed): *Control of Communicable Diseases in Man*, ed 11. New York, American Public Health Association, 1970, p 75.

36. Eichenwald HF, Ababio BA, Arky AM, et al: Epidemic diarrhea in premature and older infants caused by ECHO virus type 18. *JAMA* 166:1563-1566, 1958.

37. Klein JO, Lerner AM, Finland M: Acute gastroenteritis associated with ECHO virus, type 11. *Am J Med Sci* 240:749-753, 1960.

38. Flewett TH, Bryden AS, Davies H, et al: Epidemic viral enteritis in a long-stay children's ward. *Lancet* 1:4-5, 1975.

39. Bruck E, Abal G, Aceto T Jr: Pathogenesis and pathophysiology of hypertonic dehydration with diarrhea: A clinical study of 59 infants with observations of respiratory and renal water metabolism. *Am J Dis Child* 115:122-144, 1968.

40. Merson MH, Morris GK, Sack DA: Travelers' diarrhea in Mexico: A prospective study of physicians and family members attending a congress. *N Engl J Med* 294:1299-1305, 1976.

41. Gorbach SL, Kean BH, Evans DG, et al: Traveler diarrhea and toxigenic *Escherichia coli*. *N Engl J Med* 292:933-936, 1975.

42. Gorbach SL, Khurana CM: Toxigenic *Escherichia coli*: A cause of infantile diarrhea in Chicago. *N Engl J Med* 287:791-795, 1972.

43. Guerrant RL, Dickens MD, Wenzel RP, et al: Toxigenic bacterial diarrhea: A nursery outbreak involving multiple bacterial strains. *J Pediatr* 89:885-891, 1976.

44. Bishop RF, Davidson GP, Holmes IH, et al: Detection of a new virus by electron microscopy of faecal extracts from children with acute gastroenteritis. *Lancet* 1:149-151, 1974.

45. Flewett TH, Bryden AS, Davies H, et al: Relation between viruses from acute gastroenteritis of children and newborn calves. *Lancet* 2:61-63, 1974.

46. Middleton PJ, Szymanski MT, Abbott GD, et al: Orbivirus acute gastroenteritis of infancy. *Lancet* 1:1241-1244, 1974.

47. Kapikian AZ, Kim HW, Wyatt RG: Human reovirus-like agent as the major pathogen associated with "winter" gastroenteritis in hospitalized infants and young children. *N Engl J Med* 294:965-972, 1976.

48. Carr ME, McKendrick GD, Spyridakis T, et al: The clinical features of infantile gastroenteritis due to rotavirus. *Scand J Infect Dis* 8:241-243, 1976.

49. Rodriguez WJ, Kim HW, Arrobio JO, et al: Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children. *J Pediatr* 91:188-193, 1977.

50. Walker-Smith J: Rotavirus gastroenteritis. *Arch Dis Child* 53:355-362, 1978.

51. Tallett S, Mackenzie C, Middleton P, et al: Clinical, laboratory and epidemiologic features of a viral gastroenteritis in infants and children. *Pediatrics* 60:217-222, 1977.

52. Emery JL, Swift PGF, Worthy E: Hypernatraemia and uraemia in unexpected death in infancy. *Arch Dis Child* 49:686-692, 1974.

53. Comay S, Karabus CD: Peripheral gangrene in hypernatraemic dehydration of infancy. *Arch Dis Child* 50:616-619, 1975.

54. Metcoff J, Frenk S, Gordillo G, et al: Intracellular composition and homeostatic mechanisms in severe chronic infantile malnutrition: IV. Development and repair of the biochemical lesion. *Pediatrics* 20:317-336, 1957.

55. Gomez F, Ramos-Galvan R, Cravioto J, et al: Intracellular composition and homeostatic mechanisms in severe chronic infantile malnutrition: I. General considerations. *Pediatrics* 20:101-104, 1957.

56. Gordillo G, Soto RA, Metcoff J, et al: Intracellular composition and homeostatic mechanisms in severe chronic infantile malnutrition: III. Renal adjustments. *Pediatrics* 20:303-316, 1957.

57. Frenk S, Metcoff J, Gómez F, et al: Intracellular composition and homeostatic mechanisms in severe chronic infantile malnutrition: II. Composition of tissues. *Pediatrics* 20:105-120, 1957.

58. Metcoff J, Frenk S, Antonowicz I, et al: Relations of intracellular ions to metabolite sequences in muscle in kwashiorkor: A new reference for assessing the significance of intracellular concentrations of ions. *Pediatrics* 26:960, 1960.

59. Filer LJ Jr, Martinez GA: Intake of selected nutrients by infants in the United States: An evaluation of 4,000 representative 6-month-olds. *Clin Pediatr* 3:633-645, 1964.

60. Filer LJ Jr: Salt in infant foods. *Nutr Res* 29:27-30, 1971.

61. Puyau FA, Hampton LP: Infant feeding practices 1966: Salt content of the modern diet. *Am J Dis Child* 111:370-373, 1966.

62. Finberg L: The possible role of the physician in causing hypernatremia in infants dehydrated from diarrhea. *Pediatrics* 22:2-4, 1958.

63. Goldman HI, Freudenthal R, Holland B, et al: Clinical effects of two different levels of protein intake on low-birth-weight infants. *J Pediatr* 74:881-889, 1969.

64. Berenberg W, Mandell F, Fellers FX: Hazards of skimmed milk, unboiled and boiled. *Pediatrics* 44:734-737, 1969.

65. Coodin FJ, Gabrielson IW, Addiege JE Jr: Formula fatality. *Pediatrics* 47:438-439, 1971.

66. Stern GM, Jones RB, Fraser AC: Hyperosmolar dehydration in infancy due to faulty feeding. *Arch Dis Child* 47:468-469, 1972.

67. Taitz LS, Byers HD: High calorie/osmolar feeding and hypertonic dehydration. *Arch Dis Child* 49:257, 1974.

68. Simpson H, O'Duffy J: Need for clarity in infant feeding instructions. *Br Med J* 3:536-537, 1967.

69. Skinner AL: Water depletion associated with improperly constituted powdered milk formulas. *Pediatrics* 39:625-626, 1967.

70. Abrams CA, Phillips LL, Berkowitz C, et al: Hazards of overconcentrated milk formula: Hyperosmolality, disseminated intravascular coagulation and gangrene. *JAMA* 232:1136-1140, 1975.

71. Ruza Tarrio, FJ: *Estudio Etiopatogénico de la Trombosis Venosa Renal del Recién Nacido*, thesis. Facultad de Medecina de la Universita Autonoma de Madrid. Madrid, 1975.

72. Willard D, Messer J, deGeeter B, et al: Hyperosmolarité grave par erreur diététique chez le nouveau-né: Une pathologie particulièrement à craindre chez les migrants. *Nouv Presse Med* 5:1893-1898, 1976.

73. Smith BAM: Feeding overstrength cow's milk to babies. *Br Med J* 4:741-742, 1974.

74. Oates RK: Infant-feeding practices. *Br Med J* 2:762-764, 1973.

75. Martinez GA: Recent history and current trends, in Fomon SJ (ed): *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974, p 15.

76. Bergman KE, Ziegler EE, Fomon SJ: Water and renal solute load, in Fomon SJ (ed): *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974, chap 10, pp 245-266.

77. Davies DP: Plasma osmolality and feeding practices of healthy infants in the first three months of life. *Br Med J* 2:340-342, 1973.

78. Dale G, Goldfinch ME, Sibert JR, et al: Plasma osmolality, sodium, and urea in healthy breast-fed and bottle-fed infants in Newcastle upon Tyne. *Arch Dis Child* 50:731-734, 1975.

79. Clarke TA, Markarian M, Griswold W, et al: Hypernatremic dehydration resulting from inadequate breast-feeding. *Pediatrics* 63:931-932, 1979.

80. Whaley P, Walker-Smith JA: Hypernatraemia and gastroenteritis. *Lancet* 1:51-52, 1977.

81. Davies DP, Ansari BM, Mandal BK: Hypernatraemia and gastroenteritis. *Lancet* 1:252, 1977.

82. Davies DP, Anseri BM, Mandal BK: The declining incidence of infantile hypernatremic dehydration in Great Britain. *Am J Dis Child* 133:148-150, 1979.

83. Manuel PD, Walker-Smith JA: Infant feeding practices. *Br Med J* 2:705-706, 1978.

84. Finberg L: Hypernatremic dehydration. *Adv Pediatr* 16:325-344, 1969.

85. Habel AH, Simpson H: Osmolar relation between cerebrospinal fluid and serum in hyperosmolar hypernatraemic dehydration. *Arch Dis Child* 51:660-666, 1976.

86. Latta T: Relative to the treatment of cholera by the copious injection of aqueous and saline fluids into the veins: Letter to the Secretary of the Board of Health, London. *Lancet* 2:274, 1832.

87. Gutman RA, Drutz DJ, Whalen GE Jr, et al: Double blind fluid therapy evaluation in pediatric cholera. *Pediatrics* 44:922-931, 1969.

88. Finberg L, Cheung C, Fleishman E: The significance of the concentrations of electrolytes in stool water during infantile diarrhea. *Am J Dis Child* 100:809-813, 1960.

Neonatal von Willebrand's Disease: Diagnostic Difficulty at Birth

von Willebrand's disease (vWD) is an inherited disorder of bleeding, which is characterized by easy bruisability, mucosal hemorrhages, excessive posttraumatic bleeding, prolonged skin bleeding times, and quantitative or qualitative defects of the factor VIII molecular "complex." von Willebrand's disease and the structure and physiology of the factor VIII molecule have recently been reviewed.[1-3]

We studied a 7-month-old affected male infant whose father and paternal grandfather were known to have vWD. Because of his family history, the child's plasma was studied at birth, at 6 months of age, and after the intravenous (IV) administration of cryoprecipitate. Our findings emphasize the difficulty in establishing the diagnosis of vWD in the immediate postnatal period.

Report of a Case.—The patient is a 7-month-old boy, product of an uncomplicated 40-week gestation, born to a 19-year-old, blood group O, Rh-positive, gravida 1, para 1, abortus 0, hemostatically normal woman. Labor was induced with IV vasopressin five hours after spontaneous rupture of the membranes. Seven hours later, signs of fetal distress appeared and the patient was delivered by cesarean section. At birth, the child was dusky and had a good cry. The one- and five-minute Apgar scores were 8 and 9, respectively. Birth weight was 3,530 g. Results of physical examination were normal. His neonatal course was uneventful and diagnosis was made on the fifth hospital day.

His father and paternal grandfather have histories of life-long bleeding and are known to have vWD (Table). Because of the family history of vWD, cord blood (IgG level, 380 mg/dL; IgM level, 50 mg/dL) was obtained immediately after birth and the infant's plasma levels of factor VIII anticoagulant (FVIII-AGH), factor VIII-related antigen (FVIII-AGN), and factor VIII-risotocetin cofactor activity (VIII-vWF) were measured. At 6 months of age, he was noted to have bilateral inguinal hernias that required surgical correction. Laboratory studies at that time showed the presence of vWD (Table).

• Immediately prior to, and at six-hour intervals after surgery, 1 unit of cryoprecipitate was infused. The child's postoperative course was uneventful and he was discharged 48 hours after surgery.

Measurement of the template bleeding time, of levels of FVIII-AHG, FVIII-AGN, and FVIII-vWF, and of two-dimensional crossed immunoelectrophoresis of plasma FVIII-AGN was performed by previously described techniques.[4] Our laboratory normal values were determined by assaying plasma from 55 normal adult persons against our standard pool (20 adult donors).

Data on the patient's father and paternal grandfather revealed that both have reduced plasma levels of FVIII-AHG, FVIII-AGN, and FVIII-vWF, and prolonged template bleeding times (Table). Cord blood obtained at birth from the patient had normal plasma levels of FVIII-AHG, FVIII-AGN, and FVIII-vWF. However, when studied again at the age of 6 months, his plasma levels of FVIII-AHG, FVIII-AGN, and FVIII-vWF were found to be decreased (Table). In addition, his plasma FVIII-AGN had an increased mobility on two-dimensional immunoelectrophoresis.

After transfusion of 1 unit of cryoprecipitate on the day prior to surgery, his plasma FVIII-AHG, FVIII-AGN, and FVIII-vWF levels rose to normal. The FVIII-AHG level remained within the normal range during the entire 24-hour period of observation. The plasma levels of FVIII-vWF and FVIII-AGN returned to the pretransfusion values by eight hours and 24 hours, respectively. Bleeding time studies were not performed.

Comment.—von Willebrand's disease is a heterogenous disorder. Some patients have absent or reduced levels of FVIII-vWF, FVIII-AGN, and FVIII-AHG. In others, a defect in FVIII-vWF is associated with normal FVIII-AGN and FVIII-AHG levels.[5] Those persons may also have an FVIII-AGN whose mobility on two-dimensional crossed immunoelectrophoresis is increased.[6] Bleeding times vary and may not correlate with the levels of FVIII-AHG, FVIII-AGN, or FVIII-vWF.

Our patient's vWD is characterized by reduced levels of FVIII-AHG, FVIII-AGN, and FVIII-vWF, and an abnormal electrophoretic mobility of his plasma FVIII-AGN. In addition, he responded to cryoprecipitate infusion with the prolonged rise in FVIII-AHG characteristic of vWD.[7] His affected father and paternal grandfather have clinical bleeding, prolonged template bleeding times, and reduced FVIII-AHG, FVIII-AGN, and FVIII-vWF levels. Of interest was the observation that the child's plasma FVIII-vWF and FVIII-AGN levels fell after transfusion at rates similar to those described in adult patients with vWD.[8]

Normal term infants are reported to have normal cord blood levels of FVIII-AHG and FVIII-AGN, and, perhaps, slightly reduced levels of FVIII-vWF.[9] Of concern is that our patient's plasma levels of FVIII-

Laboratory Data Relevant to von Willebrand's Disease

	Template Bleeding Time, min	FVIII-AHG,* Units/mL	FVIII-AGN, Units/mL	FVIII-vWF, Units/mL
Paternal grandfather	> 20	0.22	0.21	0.18
Father	> 20	0.28	0.26	0.22
Patient				
At birth	ND†	0.58	1.20	1.04
At 6 mo	ND	0.33	0.23	0.23
10 min posttransfusion	ND	1.54	1.01	0.62
2 hr posttransfusion	ND	0.97	1.04	0.66
4 hr posttransfusion	ND	0.80	0.92	0.62
6½ hr posttransfusion	ND	0.82	0.81	0.52
8 hr posttransfusion	ND	0.75	0.73	0.34
12 hr posttransfusion	ND	0.81	0.66	0.33
24 hr posttransfusion	ND	0.82	0.28	0.30
Normal (55 normal adults)	< 8	> 0.62	> 0.60	> 0.45

*FVIII-AHG indicates factor VIII coagulant level; FVIII-AGN, factor VIII-related antigen; FVIII-vWF, factor VIII-ristocetin cofactor activity.
†ND indicates not done.

AHG, FVIII-AGN, and FVIII-vWF were normal at birth. Those plasma levels may rise in adult vWD patients in response to "stress," pregnancy, administration of epinephrine, or the infusion of the synthetic vasopressin analogue 1-deamino-8-D-arginine vasopressin without an improvement in the bleeding time.[1] It is possible that at birth our patient's normal plasma levels of FVIII-AHG, FVIII-AGN, and FVIII-vWF were in response to the vasopressin used to induce labor, or to his prenatal "stress."[10] These may then have obscured the diagnosis of vWD. Our observation suggests that elective diagnostic studies and surgical procedures in neonates suspected to have vWD should be delayed, when possible, beyond the neonatal period.

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1. Hoyer LW: von Willebrand's disease, in Spaet H (ed): *Progress in Hemostasis and Thrombosis*. Grune & Stratton Inc, New York, 1976, vol 3, pp 231-287.

2. Gralnick HR, Coller BS, Shulman NR, et al: Factor VIII. *Ann Intern Med* 86:598-616, 1977.

3. Ratnoff OD: Antihemophiliac factor (factor VIII). *Ann Intern Med* 88:403-409, 1978.

4. Conlon CL, Weinger RS, Cimo PL, et al: Telangiectasia and von Willebrand's disease in two families. *Ann Intern Med* 89:921-924, 1978.

5. Ekert H, Firkin BG: Recent advances in haemophilia and von Willebrand's disease. *Vox Sang* 28:409-421, 1975.

6. Gralnick HR, Coller BS, Sultan Y: Studies of the human factor VIII/von Willebrand factor protein: III. Qualitative defects in von Willebrand's disease. *J Clin Invest* 56:814-827, 1975.

7. Sultan Y, Simeon J, Maisonneuve P, et al: Immunologic studies in von Willebrand's disease: Alteration of factor VIII/von Willebrand protein after transfusion with plasma concentrates in patients with von Willebrand's disease. *Thromb Haemost* 35:110-119, 1976.

8. Chediak JR, Telfer MC, Green D: Platelet function and immunologic parameters in von Willebrand's disease following cryoprecipitate and factor VIII concentrate infusion. *Am J Med* 62:369-376, 1977.

9. Fukui H, Takase T, Ikari H, et al: Factor VIII procoagulant activity, factor VIII related antigen and von Willebrand factor in newborn cord blood. *Br J Haematol* 42:637-646, 1979.

10. Holden KR, Young RB, Piland JH, et al: Plasma pressors in the normal and stressed newborn infant. *Pediatrics* 49:495-503, 1972.

Munchausen's Syndrome

Munchausen's syndrome, or chronic factitious illness, is the diagnosis applied to a patient who chronically seeks admission to hospitals, with apparently acute illnesses. These are due to self-inflicted, self-mutilative lesions associated with misleading physical and laboratory findings as well as an exaggerated, distorted medical history. These patients are frequently dramatic in their presentation of symptoms and are often sophisticated and knowledgeable in medical terminology. As a result of their confusing, skillful mimicry, they may be subjected to many unnecessary medical and surgical procedures.

Most pediatricians have encountered malingering or such simulated symptoms as factitious fever in children and adolescents. Major chronic factitious illness or Munchausen's syndrome is very rare in the pediatric age group.[1]

Report of a Case.—The patient is a 15½-year-old girl who had been adopted at age 2 years in Japan and reared in Hawaii as an only child. Her first major hospitalization occurred at age 15½ years for headache and abdominal pain. These symptoms appeared one month after the family home was burglarized, after which the patient allegedly received threatening phone calls and reportedly was raped. A subsequent hospitalization occurred six months later for anxiety symptoms, induced by repeated threats from the assailant. Over the next year, numerous physician contacts and hospitalizations took place.

At 17 years of age, she was hospitalized for removal of an exostosis of the foot. Six months later, the patient was readmitted with a diagnosis of severe hysterical psychotic reaction and probably dissociative reaction precipitated by accumulated emotional stress. An EEG showed nonspecific abnormalities, otherwise the results of the medical workup were negative.

During the next several years, the patient was seen by a series of practitioners and specialists for a variety of complaints, the most serious of which was suspected septic arthritis of the knee that resulted in hospitalization. *Proteus* and *Escherichia coli* grew from an aspirate of the left knee. Four months after her first septic joint, she was readmitted for a recurrence. Again *E coli* grew from the aspirate. On follow-up, the patient complained of morning stiffness and arthralgias without evidence of joint swelling and received high-dose aspirin therapy. Numerous episodes of septic arthritis of the left knee recurred from which *Staphylococcus aureus*, *E coli*, and *Klebsiella* were cultured.

Later, a synovectomy and meniscectomy were performed for chronic inflammatory synovitis. At 18½ years of age, the patient again had fever and knee pain; a diagnosis of rheumatoid arthritis was entertained, and she was referred to the Rheumatology Clinic at Kapiolani-Children's Medical Center in Honolulu. Temperature was 38.5 °C. Considerable pain on movement of the left leg was noted, and her left knee was inflamed and swollen with effusion. Routine laboratory studies, as well as extensive infectious, immunologic, and rheumatologic studies were normal except for a slightly elevated anti-DNA antibody level. Culture of the joint fluid was sterile. A psychiatric consultant evaluated the patient to be a "typical, stable adolescent, without gross psychopathology."

During the next several months, the patient was hospitalized for recurrent joint pains, a suspected seizure disorder, and rectal and vaginal bleeding. A dilation and curettage (D&C) was performed. In yet another episode, the patient experienced loss of consciousness, followed by a glove-like anesthesia of the arm, and later a transient paralysis developed. During a subsequent hospitalization for a possible seizure, she complained of multiple joint pains. Her C-reactive protein and rheumatoid factor were both weakly positive.

At 19½ years, the patient was readmitted for a septic *right* knee. She gave a history of persistent morning joint stiffness of hands and shoulders for which she had been receiving high-dose aspirin therapy from her private physician. She also gave a three-week history of redness and burning in her right eye for which she had received prednisone. On physical examination, the joint was swollen, and an effusion was present. Four puncture marks lateral to the patella were noted. *Klebsiella* grew from an aspirate of the knee. Four blood cultures were negative. An extensive infectious, immunologic, and rheumatologic workup was again repeated, and results were negative.

One month after discharge, the patient returned to the center with evidence of a septic right knee, and *Klebsiella* again grew from the aspirate. Two needle marks, presumably the result of aspirations performed by her private physician, were noted. On the patient's 23rd hospital admission one month later, she complained of neck stiffness, dysphagia, and headache. At that time, she gave a history of two prior D&Cs. During the next eight months, she saw many physicians for various complaints and at 20 years of age was noted to have swelling above both wrists with associated needle marks. At this time, a syringe containing a feculent suspension was inadvertently discovered among her possessions.

In all, this patient experienced 23 hospitalizations, 13 major surgical procedures and, innumerable visits to many physicians before the correct diagnosis of Munchausen's syndrome was confirmed. Subsequently, while under psychiatric treatment, she

has recently been hospitalized for sepsis secondary to an intravenous injection of urine.

Comment.—The basic distinction between malingering, hysterical conversion reaction, and Munchausen's syndrome is often unclear. Most authorities agree that malingering is conscious, volitional, situationally appropriate behavior aimed toward clear secondary gains. It is often associated with a stressful environment; however, there are usually no major psychopathologic findings evident.[2] A conversion reaction is nonorganic illness in which the signs and symptoms are nonvolitionally simulated and secondary to unconscious drives.[3,4] Munchausen's syndrome is an underlying psychiatric disorder with an "addiction" to medical care. Organic illness is present that is self-inflicted. These medically sophisticated patients often have a bizarre history that is usually long, complex, dramatic, and plausible. They frequently are employed in an allied medical field or at least have had substantial contact with medical facilities. Motivation for their actions is usually obscure. Their need to be involved with physicians is an integral part of their personalities.[4]

In 1951, Asher named this syndrome after Baron Friedrich von Munchausen (1720-1790), a retired German cavalry officer, who wandered from town to town "telling tall tales."[5] The syndrome has been linked to many underlying psychiatric diagnoses, such as sociopathic personality disorder, schizophrenia, various psychoses, and hysterical neuroses. Early childhood trauma, possibly associated with a medical setting or some form of deprivation, is often elicited.[2,6] There may be an impressive variety of symptoms and signs. The patient's medical contacts are usually extensive. One adult patient was the subject of 16 case reports in the literature with an extensive spectrum of manifestations.[2,5,7]

Of the three reported cases in the pediatric age group, one was that of a severely disturbed adolescent girl with a long, complicated history of uterine bleeding during and after pregnancy, hematemesis after consuming blood, massive self-bloodletting, repeated anemia and shock, home storage of large quantities of blood, and hematuria from urethral trauma.[6,8] The second case was that of a 15-year-old boy who simulated an enterovesicular fistula by contamination of his urine with feces and food, at times by retrograde injection into his bladder.[9] An adolescent who produced recurrent parotitis by insufflation of his Stensen's ducts has been described. Munchausen's syndrome by proxy has been reported in the pediatric age group.[10,11] Here, children are the victims of factitious illness inflicted on them by parents or caretakers.

The diagnosis in our case was difficult because of the patient's seemingly genuine complaints and perplexing findings. This girl was an excellent student, was involved in extracurricular activities, and had worked with arthritic patients in an orthopedist's office for a year as a physical therapy aide. She was well read, familiar with medical procedures and terminology, and highly informed on the subject of rheumatoid arthritis, the symptoms of which she incorporated in her presentations. However, the organisms cultured from her joint aspirates were highly atypical for septic joints in this age group and provided the clue to the correct diagnosis.[12,13]

Once exposed, adult patients usually leave the hospital abruptly and exhibit some form of contempt or antisocial behavior toward personnel caring for them.[14] Although it is easy to become frustrated managing a patient suspected of having factitious illness, these patients have a severe, life-threatening psychiatric illness requiring intervention. The rarity of Munchausen's syndrome in childhood and adolescence predisposes to diagnostic and treatment problems. Often there are associated moral, ethical, and legal dilemmas. The deviant physician-patient relationship contains no therapeutic alliance, and adult patients usually avoid psychiatric help. In minors, therapy can be enforced with parental cooperation. However, the parents themselves may undergo intense feelings of grief and helplessness. They may find the suggestion of chronic factitious illness in their child absurd, and bring litigation against physicians for unnecessary procedures performed on their child. Judicial intervention may be necessary to obtain proper protection and psychiatric treatment.

Munchausen's syndrome is rare and often belatedly considered as a possible diagnosis. The actual incidence is unknown. In the adolescent, accurate medical diagnosis is often obscured by behavioral and emotional problems, and depression with somatization. Making the diagnosis requires a high index of suspicion, close scrutiny of prior medical contacts, and effective communication among health care deliverers.

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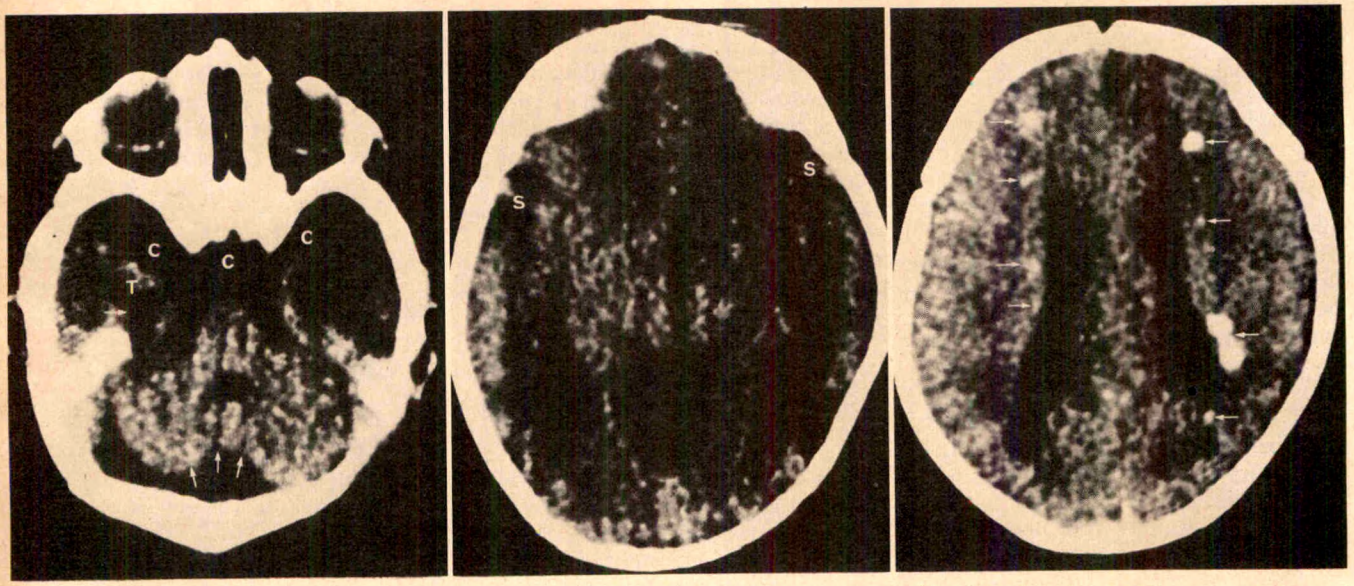
1. Herzberg JH, Wolff SM: Chronic factitious fever in puberty and adolescence: A diagnostic challenge to the family physician. *Psychiatry Med* 3:205-212, 1972.
2. Spiro HR: Chronic factitious illness. *Arch Gen Psychiatry* 18:569-579, 1968.
3. Ananth J: Munchausen syndrome: Problematic diagnosis. *NY State J Med* 77:115-117, 1977.
4. Cramer B, Gershberg MR, Stern M: Munchausen syndrome: Its relationship to malingering, hysteria, and the physician-patient relationship. *Arch Gen Psychiatry* 24:573-578, 1971.
5. Asher R: Munchausen's syndrome. *Lancet* 1:339-341, 1951.
6. Ireland P, Sapira JD, Templeton B: Munchausen's syndrome: Review and report of an additional case. *Am J Med* 43:579-592, 1967.
7. Sjoberg S: Munchausen's syndrome. *Lancet* 1:1073, 1951.
8. Steinbeck AW: Hemorrhagica historionica—The bleeding Munchausen syndrome. *Med J Aust* 48:451-456, 1961.
9. Reich P, Lazarus JM, Kelly MJ: Factitious feculent urine in an adolescent boy. *JAMA* 238:420-421, 1977.
10. Meadow R: Munchausen syndrome by proxy: The hinterland of child abuse. *Lancet* 2:343-345, 1977.
11. Kurlandsky L, Lukoff J, Zinkham W: Munchausen syndrome by proxy: Definition of factitious bleeding in an infant by ^{51}Cr labeling of erythrocytes. *Pediatrics* 63:228-231, 1979.
12. Borella L, Goobar JE, Summitt RL: Septic arthritis in childhood. *J Pediatr* 62:742-747, 1963.
13. Nelson JD, Koontz WC: Septic arthritis in infants and children: A review of 117 cases. *Pediatrics* 38:966-971, 1966.
14. Clarke E, Melnick SC: The Munchausen syndrome or the problem of hospital hoboes. *Am J Med* 25:6-12, 1958.

Computerized Tomography to Define CNS Involvement in Congenital Cytomegalovirus Infection

The most serious sequelae of congenital cytomegalovirus (CMV) infection involve the CNS. However, predicting the neurological outcome of a neonate with congenital CMV may be difficult unless severe CNS damage is already obvious at birth. Some severely affected babies with intrauterine growth retardation, hepatosplenomegaly, and other stigmata asso-



Computerized tomographic scan of infant with congenital cytomegalovirus infection done at 1 week of age showing cerebellar atrophy (arrows), dilated temporal horns (T) and enlarged cisterns (C) (left); large subarachnoid space (S) and hydrocephalus (center); and periventricular calcifications (arrows) (right).

ciated with CMV infection have normal intellectual development without detectable neurological deficits.[1] Neurological evaluation usually consists of a careful neurological examination and a roentgenogram of the skull to detect calcifications. We describe a newborn with proven congenital CMV infection who had a normal neurological examination and a normal roentgenogram of the skull; computerized tomography (CT) gave a more accurate picture of the severity of CNS involvement.

Report of a Case.—A full-term baby girl was born to a 28-year-old-mother who had a negative test for syphilis and a positive rubella titer. The baby weighed 2,110 g and had an Apgar score of 7 at one minute, and 8 at five minutes. Height, weight, and head circumference measurements were all below the fifth percentile. The head circumference was 35.0 cm and was proportional to the height and weight. Physical examination revealed a small-for-gestational age baby with marked jaundice, numerous "blueberry muffin"-type skin lesions, petechiae, and hepatosplenomegaly. Results of ophthalmologic and neurologic examinations and audiometry (behavioral response to pure tones) were normal. The peripheral WBC count was 7,700/cu mm; platelet count was 1,000/cu mm; and SGOT level was 98 IU/L (normal newborn value, 16 to 74 IU/L). Bacterial cultures of CSF, blood, throat, and stool were sterile or revealed no pathogens. Cytomegalovirus grew from viral cultures of urine and nasopharynx. Roentgenograms of the knees and wrists revealed metaphyseal rarefactions and "celery stalking" of the femurs and tibias consistent with intrauterine infection. A roentgenogram of the skull were normal; intracranial calcifications were not seen.

The baby's skin lesions, jaundice, heptosplenomegaly, and thrombocytopenia gradually resolved over a three-week period. Because of concern that severe thrombocytopenia may have predisposed the child to an occult intracranial hemorrhage, a CT scan was done (Figure). The CT scan showed mild hydrocephalus of the entire ventricular system. The subarachnoid space was voluminous, most noticeable over the left side of the cerebellum. There was no midline shift. Extensive periventricular calcium was identified.

At 1 month of age, the baby was seen in the outpatient clinic because of a generalized seizure, and treatment with phenobarbital was begun. At 5 months of age, the child had poor head control and did not roll over.

Comment.—Babies with congenital CMV infection who have microcephaly, seizures, or other findings of serious CNS involvement at birth have a poor prognosis in terms of future neurological development.[1-4] At least 75% will have microcephaly, psychomotor retardation, deafness, seizures, or other major cerebral dysfunction in later years.[5] Intracranial calcifications shown by plain roentgenograms of the skull suggest extensive brain involvement and are a poor prognostic sign[1,3] but are present in less than 1% of newborns with CMV.[4,5]

Our patient had clinical and laboratory evidence of severe, generalized CMF infection, but her neurologic examination and skull roentgenograms were normal in the neonatal period, suggesting a good prognosis. The CT examination was helpful in defining the true extent of CNS involvement.

Computerized tomography is more sensitive than plain films in demonstrating intracranial calcifications.[6-8] Also CT scan may reveal enlargement of the ventricular system and other abnormalities of the brain substance that are not visible on plain films. In the initial evaluation of babies with suspected intrauterine infection, particularly congenital CMV and toxoplasmosis, CT scan should be considered if plain roentgenographs are normal. The detection of calcifications or other brain abnormalities may be helpful in establishing the diagnosis of congenital infection early, and in clarifying the severity of neurologic involvement and thus the child's prognosis.

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1. Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, WB Saunders Co, 1976, pp 107-155.

2. Weller TH, Hanshaw JB: Virological and clinical observations of cytomegalic inclusion disease. *N Engl J Med* 266:1233-1244, 1962.

3. Hanshaw JB: Congenital cytomegalovirus: A 15-year prospective. *J Infect Dis* 123:555-560, 1971.

4. Melish ME, Hanshaw JB: Congenital cytomegalovirus infection: Developmental progress of infants detected by routine screening. *Am J Dis Child* 126:190-194, 1973.

5. Haymaker W, Girdany B, Stephens J, et al: Cerebral involvement with advanced periventricular calcification in generalized cytomegalic inclusion disease in the newborn. *J Neuropathol Exp Neurol* 13:562-586, 1954.

6. New PFJ, Scott WR, Schnur JA, et al: Computed tomography with the EMI scanner in the diagnosis of primary and metastatic intracranial neoplasms. *Radiology* 114:75-87, 1975.

7. Ambrose J: Computerized transverse axial scanning (tomography):II. Clinical application. *Br J Radiol* 46:1023-1047, 1973.

8. Gawler J, Bull JWD, Boulay GH Jr, et al: Computer-assisted tomography (EMI Scanner): Its place in investigation of suspected intracranial tumours. *Lancet* 2:419-423, 1974.

Heparin-Precipitable Cryoprecipitate in a Child With Cold Urticaria

Cold urticaria occurs occasionally in childhood and is associated at times with cryoglobulinemia, cold hemolysins, or cryofibrinogenemia. We describe here a patient who has cold urticaria associated with increased levels of heparin sodium-precipitable cryoprecipitate (HPC); to our knowledge, such a case has not been previously reported.

Report of a Case.—A 10-year-old girl was first seen in November 1976 because of urticaria accompanied by arthralgia. The previously well child had an intensely pruritic eruption of the feet develop after a swimming lesson. This resolved spontaneously within eight hours. Two days later, urticaria was noted from the waist to the feet after attendance at a night football game. Subsequent long outdoor exposures induced urticaria on the trunk, face, and legs and swelling of the fingers. Occasionally, the eruptions were accompanied by pain in the hips, shoulders, and right ankle. Cyproheptadine hydrochloride therapy did not diminish the urticaria. The history was unremarkable, including no joint symptoms or atopic manifestations. The family history was negative for atopic disease, urticaria, or cold intolerance.

Examination showed no abnormalities except for several small, nontender supraclavicular lymph nodes. There was no dermographism, and ice-cube application did not induce urticaria.

The ESR was 100 mm/hr; IgG, 2,800 mg/dL; IgA, 400 mg/dL; IgM, 85 mg/dL; IgD, 1 mg/dL; and IgE, elevated to 740 units. Normal or negative results were obtained for the following studies: complete blood cell count, platelet count, C-reactive protein, antinuclear antibody, lupus erythematosus cell preparation, DNA binding, latex rheumatoid factor, C3, C4, total hemolytic complement, VDRL, cold agglutinins, antistreptolysin O titer, urinalysis, fibrin split products, 12-factor automated chemical analysis, fibrinogen, prothrombin time, partial thromboplastin time, α_1-antitrypsin, and serum protein electrophoresis. Chest roentgenogram showed no abnormalities.

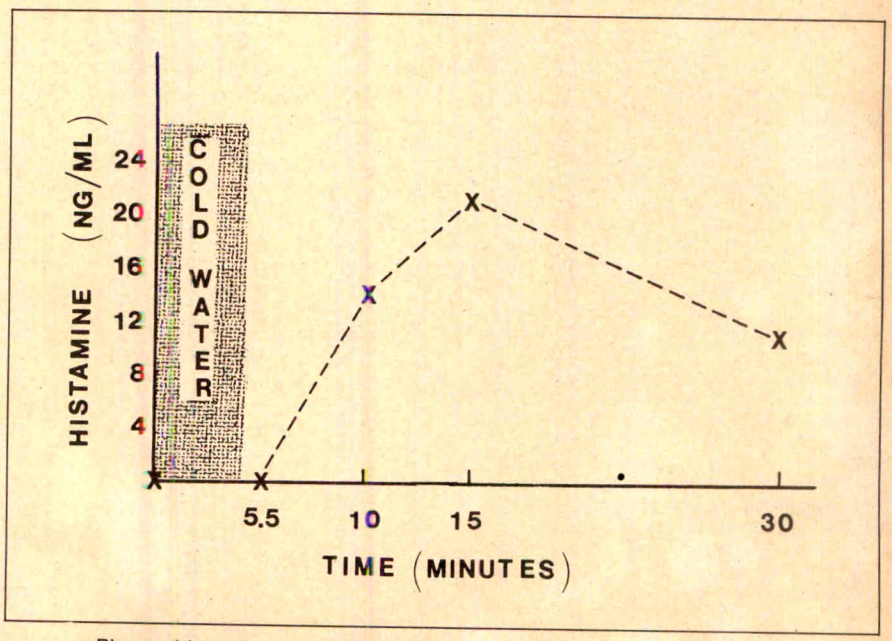
With careful protection against the cold, the patient remained clinically well during the subsequent year. However, the ESR remained greater than 50 mm/hr and plasma IgE continued to be elevated.

Special Studies.—Blood collected in preheated syringes and tubes was centrifuged at 37 °C. No notable precipitate developed in serum, heparinized plasma, or citrated plasma held at 37 °C for up to 72 hours or in serum or citrated plasma stored at 4 °C during this period of time. However, after 18 hours or more at 4 °C, heparinized plasma specimens were filled with a gelatinous precipitate. This HPC was washed twice in iced 0.05M phosphate buffer, with a pH of 7.4, and was redissolved by warming to 37 °C. The HPC specimens obtained on Nov 15, 1976, Nov 30, 1976, and Jan 26, 1977 showed total protein values (Lowry method) of 245, 125, and 200 mg/dL of plasma from which the precipitate was obtained. Respective fibrinogen measurements, by thrombin clotting time, in the redissolved HPC samples were 17, 25, and 39 mg/dL. A fourth specimen obtained in June 1977 showed an HPC value of 196 mg/dL. Trace amounts of immunoglobulins and complement components were detected in only one specimen. A drop of dilute thrombin solution caused immediate clotting. Immunoelectrophoresis also consistently showed a band of fibrinogen in all specimens, whereas immunoglobulins, C3, C4, and fibrin were not regularly identified. Polyacrylamide gel electrophoresis, with and without sodium dodecyl sulfate, showed a large number of components. The quantity of IgM, IgD, IgE, C3, and C4 and the hemolytic complement activity were as great in the precipitate supernatant of the second sampling (Nov 30, 1976) as in the whole plasma, and the IgG and IgA levels were only minimally reduced.

We measured HPC levels in ten other children aged 6 to 18 years. The range of values obtained was 40 to 152 mg/dL, with a mean of 95 mg/dL ± 29 SD. Thus, the patient's values on three occasions exceeded our normal values. Preferential adherence of IgE to the patient's HPC could not be demonstrated in experiments where IgE labeled with iodine 125 was added to the heparinized plasma before storage in the cold. Toluidine blue stained the well-washed cryoprecipitate, suggesting either adherence or incorporation of heparin into the precipitate.

Immersion of the left forearm in an ice water bath produced a substantial increase in the plasma histamine level[1] in venous blood drawn from the left antecubital fossa (Figure). No important change was observed in values for plasma hemolytic complement, C3, or C4 during this procedure. Changes in the HPC level were not measured. No substantial histamine release was observed in vitro at 4 °C by incubating the patient's leukocytes with her own or normal plasma or by incubating normal leukocytes with her chilled plasma.

Comment.—Hives associated with cryofibrinogenemia have been reported only rarely, though swelling of the extremities in infants has been noted.[2] In these cases, a precipitate occurs when incubating either citrated or heparinized plasma in the



Plasma histamine levels after immersion of an extremity in ice water.

cold.[3] Cryoprecipitation of plasma only in the presence of heparin is characteristic of HPC. Stathakis and Mosesson recently demonstrated that cold insoluble globulin (CIg), a normal plasma glycoprotein, is the essential element for heparin-induced cryoprecipitation of plasma.[4] However, fibrinogen substantially augments the process by its affinity for CIg. When screening more than 700 individuals for HPC, Smith found the highest values in patients with inflammatory conditions and advanced neoplasms.[5] The cause for the HPC in our patient cannot be determined from the available information since repeated studies failed to document the presence of any connective tissue or neoplastic disease. In addition, the relationship between the child's HPC and cold urticaria is uncertain. No evidence was found for complement activation, as occurs in some cases of cryoglobulinemia.[6] Other possibilities include the involvement of IgE, as in some cases of idiopathic acquired urticaria,[7] or the release of histamine from cutaneous mast cells[8] by this particular HPC. A chance association also cannot be excluded. Screening larger numbers of patients with cold urticaria for HPC may help to clarify this matter.

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1. Salberg DH, Hough LB, Kaplan DE, et al: A reverse double-isotope enzymatic histamine assay: Advantages over single-isotope methods. *Life Sci* 21:1439-1446, 1977.

2. Robinson MG, Troiano G, Cohen H, et al: Acute transient cryofibrinogenemia in infants. *J Pediatr* 69:35-39, 1966.

3. Moroz LA, Rose B: The cryopathies, in Samter M (ed): *Immunological Diseases*. Boston, Little Brown & Co, 1971, p 459.

4. Stathakis NE, Mosesson MW: Interactions among heparin, cold-insoluble globulin, and fibrinogen in formation of the heparin-precipitable fraction of plasma. *J Clin Invest* 60:855-865, 1977.

5. Smith RT: A heparin-precipitable fraction of human plasma: II. Occurrence and significance of the fraction in normal individuals and in various disease states. *J Clin Invest* 36:605-616, 1957.

6. Costanzi JJ, Coltman CA Jr, Donaldson VH: Activation of complement by a monoclonal cryoglobulin associated with cold urticaria. *J Lab Clin Med* 74:902-910, 1969.

7. Houser D, Arbesman CE, Ito K, et al: Cold urticaria: Immunologic studies. *Am J Med* 49:23-33, 1970.

8. Kaplan AP, Gray L, Shaff RE, et al: In vivo studies of mediator release in cold urticaria and cholinergic urticaria. *J Allergy Clin Immunol* 55:394-402, 1975.

Ring Chromosome 15 and Failure to Thrive

Ring chromosomes are rare in man. Friedrich and Nielson[1] could not find one ring in the compiled data of the cytogenetic screening of 31,801 consecutive live-born children. Hecht and Vlietinck,[2] as well as Zdansky et al,[3] claim that the phenotypic and cytogenetic differences among even "identical rings" do not permit an accurate delineation of an identifiable syndrome. On the other hand, certain ring chromosome syndromes (ring 1, 6, 9, 13, 15, 21, and 22) appear already in textbooks[4] as separate clinical entities. To solve the controversy, more case reports seem warranted. Therefore, we discuss an infant with ring 15.

Report of a Case.—This girl was a product of the second pregnancy for her mother, who was 161 cm tall and 27 years of age at that time. The father was 168 cm tall and 35 years of age. Illness, exposure to drugs, and roentgenograms during the pregnancy were denied. The delivery was by spontaneous breech at 43 weeks' gestation. The birth weight was 2,850 g (the first-born brother weighed 3,150 g). The length was 48 cm and the head circumference was 33 cm. The Apgar scores were recorded as 7 at one minute and 9 at five minutes. No prenatal problems were encountered but several stigmata were noted: two small nevi flammei on the forehead; a port-wine mark, 2 × 1.5 cm, on the right forearm, three small café au lait spots in the left lower axilla and a larger one, 4 × 3 cm, on the left foot, and high-arched palate. At the age of 4 months, the child was hospitalized for "failure to thrive" with poor appetite, weight loss, occasional vomiting, and fever. Her weight was 5,400 g (10th percentile), length was 55 cm (below the third percentile), and the head circumference was 37 cm (below the third percentile). There was nothing striking in her appearance. Chest, cardiovascular system, abdomen, and genitals were unremarkable. Generalized mild hypotonia was present. Deep tendon reflexes were +2 all over. The stigmata recorded at birth were less conspicuous.

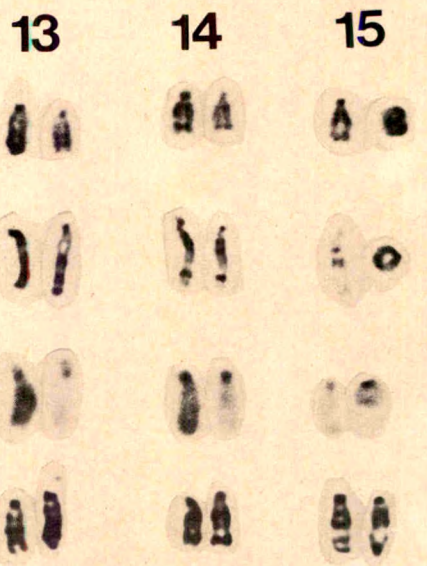
The dermatoglyphic pattern showed nine whorls and one ulnar loop. Axial triradii were in the t′ position with a bridged simian crease on the right palm only and distal loops in both third interdigital areas. Hallucal areas showed distal loops; the great toes had arches (mother and brother had similar dermatoglyphics but no simian crease).

The evaluation was nondiagnostic, the fever subsided, appetite improved, and the child was discharged home, gaining slowly in weight.

Psychological testing was done at 7 months of age. On the Bayley Scales of Infant Development, the mental age was 5 months and the motor age was 4 months; this was interpreted as mild to moderate delay in psychomotor development. Height and head circumference were below the third percentile—59 and 38.5 cm, respectively; weight was 6,300 g (third percentile).

Cytogenetic Studies.—Slides were made from peripheral blood lymphocytes of the patient and from the mother on two occasions. The mother had a normal karyotype. The father could not be studied. Seventy-five mitoses were studied: 70 of them showed 46 chromosomes with D-group chromosome replaced by a ring. The trypsin Giemsa banding technique demonstrated that the ring was formed by one of the number 15 chromosomes—46,XXr(15). It appeared that only tiny pieces of both the short and the long arm were missing. As suggested by the bands on the ring, the breakage point on the long arm was on the terminal, telometric part-q25. The short arm was not seen, which implied that the breakage point was at p11. The quinacrine fluorescent banding confirmed this impression. The C banding demonstrated one centromere on the ring. Two mitoses showed a dicentric ring in figure 8-shaped formation. One mitosis demonstrated the ring unfolded (Figure).

In none of the mitoses was the ring found in satellite association. This sug-



Partial karyotype of the patient demonstrating D-group chromosomes with centromere on ring 15, unfolded ring, and figure 8-shaped dicentric ring.

gests that the breakage point on the short arm was at p11 with the loss of the nucleolus organizer region. The latter region is known to be responsible for satellite associations for the acrocentric chromosomes in metaphase. The origin of the ring chromosome could not be determined cytogenetically.

Comment.—To the best of our knowledge, there are reports of nine patients with ring 15.[5-13] Failure to thrive was the hallmark in all those patients and growth retardation was present at birth. In our patient, however, the latter was not present. The patient of Emberger et al[6] was born at 34 weeks weighing, 2,250 g; thus, his failure to thrive also could be considered of postnatal onset. Microcephaly has been encountered in most of the patients[5,6,8,10-13] and is present in our patient as well. Mental retardation has been found in the majority of the cases.[5,6,8,11,13] The patient described by Forabosco et al[7] was considered to be of normal intelligence but she has not had formal testing and was only 16 months of age at the time of the report. The patient of Fujita and Matsomoto[12] had borderline intelligence. Based on the psychomotor delay in our patient, mental retardation should be expected. The stigmata in all patients were few and rather nonspecific. Actually, the only consistent finding was the absence of true dysmorphia.[4] Micrognathia was found in three patients.[8,11,13] Hypertelorism was claimed by three authors.[8,9,12] Including our patient, café au lait pigmentations were found in three cases.[10,12] Brachymesophalangy was seen in two patients.[7,11] A variety of stigmata was encountered just once. Major anomalies have been seen in several patients: congenital heart defects in three,[5,12,13] pyloric stenosis in one,[7] renal anomaly in one,[13] and hydrocephaly with amyotrophy in another.[8] Forabosco et al[7] and Schmid et al[11] reported the dermatoglyphics in detail without finding a characteristic pattern; other authors reported them as normal.[6,8,10,12] Our patient demonstrated only a bridged simian line in addition to the dermatoglyphic pattern characteristic for first-degree relatives examined by us.

Antenatal and/or postnatal growth deficiency may be the sole major sign of some of the newest cytogenetic syndromes, ring 15 included. Pediatricians caring for patients with failure to thrive that remains of unknown cause despite adequate workup should consider chromosomal abnormality. With banding techniques, a karyotype may demonstrate ring 15 or some other ring chromosome, such as ring 1, ring 6, or even partial 8p trisomy, as the reason for the growth deficiency.

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1. Friedrich U, Nielson J: Chromosome studies in 5,049 consecutive newborn children. *Clin Genet* 4:333-343, 1973.

2. Hecht F, Vlietinck RF: Autosomal rings and variable phenotypes. *Hum Genet* 18:99-100, 1973.

3. Zdansky R, Andre M, Bühler E, et al: Irregular phenotypic expression of ring chromosomes. *Hum Genet* 16:193-198, 1975.

4. DeGrouchy J, Turleau C: *Clinical Atlas of Human Chromosomes*. New York, John Wiley & Sons, 1977.

5. Jacobsen P: A ring chromosome in the 13-15 group associated with microcephalic dwarfism, mental retardation and emotional immaturity. *Hereditas* 55:188-191, 1966.

6. Emberger JM, Rossi D, Jean R, et al: Etude d'une observation de chromosome du group 13-15 en anneau (46,XY, 15r). *Hum Genet* 11:295-299, 1971.

7. Forabosco A, Dutrillaux B, Vazzoler G, et al: Chromosome 15 en anneau; r(15): Identification a dénuturation ménageé. *Ann Genet* 15:267-270, 1972.

8. Stoll C, Juif JG, Luckel JC, et al: Ring chromosome 15:r(15): Identification by R banding. *Hum Genet* 27:259-262, 1975.

9. Rumenić L, Joksimović I, Anaf M: Ring chromosome 15 in child with a minor dysmorphism of phenotype. *Hum Genet* 33:187-188, 1976.

10. Pfeiffer RA, Dhadial R, Lenz W: 46,XX/46,XX,r(15) mosaicism: Report of a case. *J Med Genet* 14:63-65, 1977.

11. Schmid M, Henrichs I, Nestler H, et al: Analysis of banding patterns and mosaic configurations in a case of ring chromosome 15. *Hum Genet* 41:289-299, 1978.

12. Fujita H, Matsomoto H: Ring chromosome 15; 46,XX,r(15) (p11q26) in a girl. *Jpn J Hum Genet* 23:233-237, 1978.

13. Kawasaki T, Kamimae A, Maeda J, et al: A case with No. 15 ring chromosome (Japanese). *J Pediatr Prac* 38:544, 1975.

Massive Intracranial Air Embolism: A Complication of Mechanical Ventilation

Mechanical ventilation in the management of neonates with respiratory distress syndrome has been extended to include the very premature infant weighing less than 1,001 g.[1] In spite of the new techniques and improved understanding of mechanical ventilation, there have been a number of complications.[2-5] These include pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, venous and/or arterial air embolism, pulmonary interstitial emphysema, pseudocyst formation, and bronchopulmonary dysplasia. This communication reports yet another complication, an unusual case of massive intracranial air embolism in a premature infant.

Report of a Case.—The patient was a 780-g male neonate, born spontaneously at 24 weeks' gestation. The Apgar scores at one and five minutes were 2 and 3, respectively. The infant was resuscitated by endotracheal intubation, manual bag ventilation with 1.0 fraction of inspired oxygen (Fio_2), and administration of sodium bicarbonate, epinephrine, and 5% plasma protein fraction (human) through the umbilical arterial catheter. An initial blood sample showed a Pao_2 of 32 mm Hg, a $Paco_2$ of 50 mm Hg, and a pH of 7.23. On transfer to the intensive care unit at 1½ hours of age, treatment with a pneumatically operated, time-cycled pressure ventilator was begun, using a peak inspiratory pressure of 25 cm H_2O, positive end-expiratory pressure of cm H_2O, at a rate of 30 per minute, Fio_2 of 1.0, and an inspiratory-expiratory ratio of 1:2. The Pao_2 was now 62 mm Hg; the $Paco_2$, 54 mm Hg; the pH, 7.18; and the base deficit, −9.2 mEq/L.

Initial chest roentgenogram showed bilateral coarse granular pattern and diffuse aeration disturbance bilaterally. The patient's clinical condition remained poor despite supportive therapy, and a blood sample taken at three hours after admission revealed a Pao_2 of 39 mm Hg, a $Paco_2$ of 131 mm Hg, a pH of 7.46, and a base excess of +9.2 mEq/L. The peak inspiratory pressure was gradually increased to 34 cm H_2O while the other respirator settings remained the same.

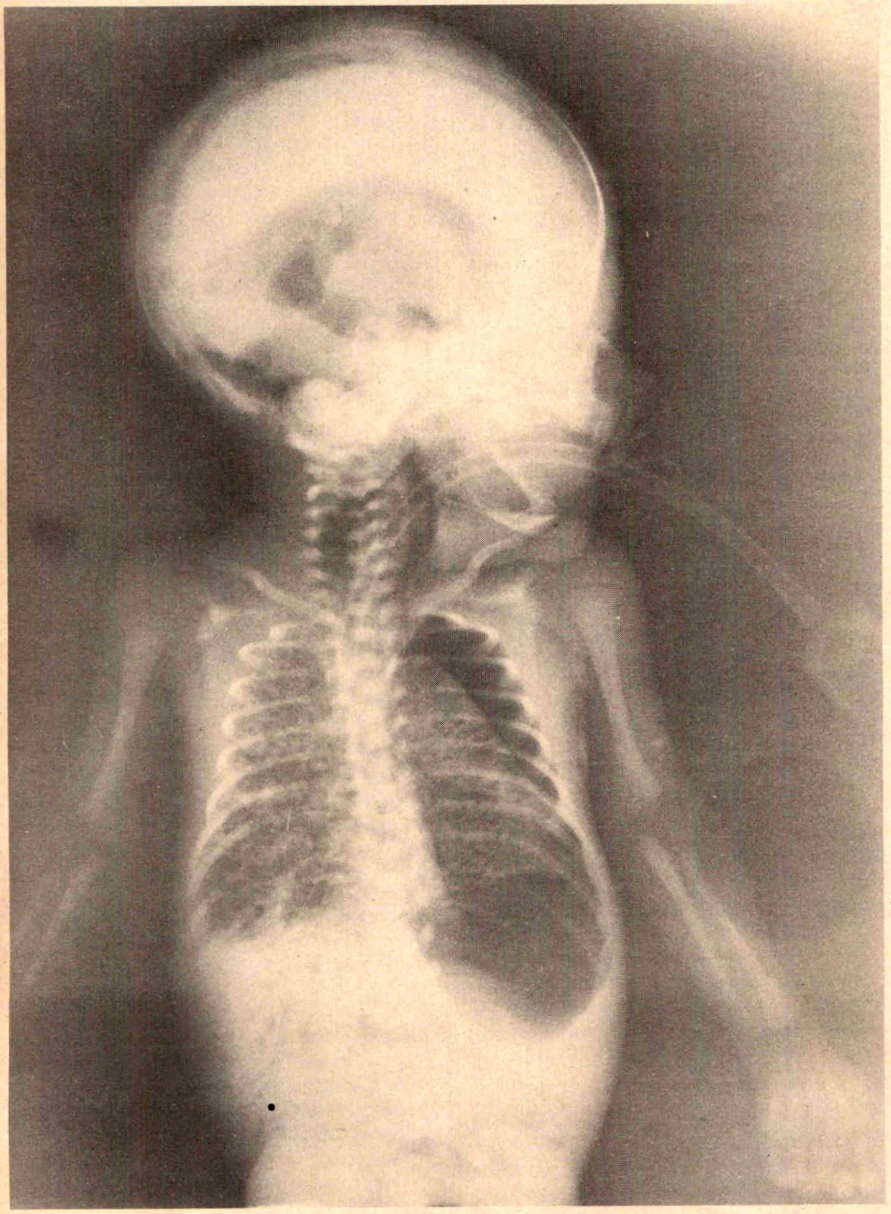
A repeated chest roentgenogram showed some improvement in the aeration of both lungs but no evidence of pneumothorax. Ten hours after admission, the heart rate dropped to 20 beats per minute. Cardiopulmonary resuscitation was immediately instituted. Substantial amounts of air in the form of bubbly, dark blood were noted on aspiration of the umbilical arterial line prior to giving sodium bicarbonate and epinephrine. An umbilical venous catheter was immediately inserted and the medications were given through this route. Very bubbly, dark blood was also noted from the umbilical venous line. Transillumination of the chest using a mini-light portable illuminator with a flexible optic light probe showed a left-sided pneumothorax. Sixty milliliters of air was obtained from the left pleural cavity by needle aspiration. The heart stopped beating and further efforts to resuscitate the infant were unsuccessful. A whole body roentgenogram taken ten minutes postmortem revealed pulmonary interstitial emphysema bilaterally and a tension pneumothorax on the left side as shown in the Figure. There was air in the hepatic veins, inferior vena cava, and in the vasculature of the neck. A considerable collection of air in the superior sagittal

sinus, cisterna magna, and lateral ventricles of the brain was also noted.

Autopsy Findings.—On autopsy, the combined weight of the lungs was 26.7 g. They were atelectatic, and crepitance was noted on the surface. Microscopic examination showed few alveoli lined by hyaline membrane. The alveolar airways were small and the lungs consisted preponderantly of interstitial tissue and alveolar pneumatocytes. The brain weighed 60 g, and it was normal in appearance on gross examination. Microscopic examination of the brain was unremarkable.

Comment.—Gas in the fetal skull as a sign of intrauterine death was described by Northway and Walls.[6] Henderson-Smart[7] reported a case of massive air embolism that included the presence of air in the cerebral venous sinuses of an infant that was detected by routine postmortem roentgenogram. Quisling et al,[8] in a series of postmortem roentgenograms obtained on 22 premature infants, were able to demonstrate progressive and spontaneous intracranial gas accumulation. In one case they noted the accumulation of gas in the subarachnoid and intraventricular spaces one hour after death. In another case this spontaneous accumulation of gas in the intracerebral veins and sinuses was not noted until four hours after death.

In our patient, the presence of intracranial gas was probably due to a massive embolic phenomenon rather than that of a spontaneous postmortem accumulation of gas. Unlike most routine postmortem roentgenograms, this infant's whole body roentgenogram demonstrating massive intravascular and intracranial gas was taken immediately after death. Also, clinical evidence of intravascular air embolism was noted by aspiration of foamy blood from the arterial and the venous catheter. Massive formation of extraventilatory air[3] with possible embolization into the brain should be suspected when air bubbles are noted in the blood from the umbilical vessel catheter, provided all tubings and connections have been checked and found to be intact. Gas in the veins of the head and in the sinuses of the dura mater could escape into the adjacent subarachnoid space thus leading to intracranial accumulation of air. Intracranial air embolism, an unusual and catastrophic complication, will probably be observed with increasing frequency with the widespread use of ventilatory assistance in the very premature neonates.



Whole body roentgenogram taken ten minutes postmortem showing considerable collection of air in the superior sagittal sinus, cisterna magna, lateral ventricles, vascular structure of the neck, left pleural cavity, hepatic veins, and inferior vena cava.

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Jeffrey Watters, MD, interpreted the roentgenographic findings and Larry Bernstein, MD, performed the postmortem examination.

1. Fitzhardinge PM, Pape K, Arstikaitis M, et al: Mechanical ventilation of infants of less than 1,501 g birth weight: Health, growth and neurologic sequelae. *J Pediatr* 88:531-541, 1976.
2. Bowen FW Jr, Chandra R, Avery GB: Pulmonary interstitial emphysema with gas embolism in hyaline membrane disease. *Am J Dis Child* 126:117-118, 1973.
3. Brown ZA, Clark JM, Jung AL: Systemic gas embolus: A discussion of its pathogenesis in the neonate, with a review of the literature. *Am J Dis Child* 131:984-985, 1977.
4. Chopra DR, Baker PC, Beam CW, et al: Arteriovenous air embolism: A complication of mechanical ventilation in respiratory distress syndrome. *Clin Pediatr* 15:178-180, 1976.
5. Weller MH: The roentgenographic course and complications of hyaline membrane disease. *Pediatr Clin North Am* 20:381-406, 1973.
6. Northway WH, Walls WL: Gas in the fetal skull: A new sign of intrauterine fetal death. *Am J Roentgenol* 89:1080-1083, 1963.
7. Henderson-Smart DJ: Massive air embolism in a neonate with respiratory distress. *Med J Aust* 2:641-642, 1975.
8. Quisling RG, Poznanski AK, Roloff DW, et al: Postmortem gas accumulation in premature infants. *Radiology* 113:155-159, 1974.

Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

Antibiotic-Resistant Streptococci

Sir.—In a recent issue of the JOURNAL (133:1143-1145, 1979), Maruyama et al reported a high percent of group A streptococci in Japan to be resistant to erythromycin and other antibiotics during a one-year survey (1974-1975). They concluded that widespread resistance might be related to excessive use of erythromycin in streptococcal therapy. We have also encountered erythromycin-resistant streptococci at our institution.

Report of a Case.—A 5-year-old boy with a sore throat was given oral penicillin V, 250 mg four times daily for ten days, after isolation of group A β-hemolytic streptococcus on culture of throat material (sheep-blood agar with bacitracin disk for presumptive group A identification). Symptoms abated within six days. Follow-up throat cultures at 13 and 20 days after the original diagnosis were still positive for group A β-hemolytic streptococcus, and therapy with penicillin was continued for a total of 27 days. A culture at 31 days was also positive, but the patient was asymptomatic (suggesting a carrier state[1]) and therapy with antibiotics was discontinued. A second culture was done at 33 days. Bacterial sensitivities (by Kirby-Bauer method[2]) showed the organism to be erythromycin-resistant, but sensitive to penicillin, oxacillin, cephalothin sodium, ampicillin sodium, and tetracycline.

Comment.—Erythromycin had not been used in this patient, either during these streptococcus-positive weeks or previously. In the eight weeks since the isolation of streptococcus from this patient, our laboratory performed susceptibility tests on 100 positive pharyngeal cultures from our clinic. Of 100 isolates, 22 were erythromycin-resistant; all were penicillin-sensitive.

Erythromycin-resistant streptococci have been reported in the United States previously.[3,4] However, in view of the experience in Japan and in view of the frequent use made of this antibiotic as a second-line drug in the treatment of streptococcal pharyngitis (and its acceptance by the American Heart Association for prevention of rheumatic fever), clinicians need to know whether or not the drug they prescribe will be effective. We should monitor the antibiotic susceptibility of cultured streptococci and perform follow-up throat cultures.

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Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-S for Injection.*
Cephalothin sodium—*Keflin.*

1. Markowitz M: Streptococcal infections, in Rudolph AM, Barnett HL, Einhorn AH (eds): *Pediatrics*, ed 16. New York, Appleton-Century-Crofts, 1977, p 501.
2. Bauer AW, Kirby W, Shervis JC, et al: Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 45:493-496, 1966.
3. Sanders E, Foster MT, Scott D: Group A β-hemolytic streptococci resistant to erythromycin and lincomycin. *N Engl J Med* 278:538-540, 1968.
4. Drapkin MS, Karchmer AW, Moellering RC Jr: Bacteremic infections due to clindamycin-resistant streptococci. *JAMA* 236:263-267, 1976.

Crouzon's Disease Data

Sir.—I read with great interest the article by Powazek and Billmeier entitled "Assessment of Intellectual Development after Surgery for Craniofacial Disorders" (JOURNAL 133:151-153, 1979).

I have seen a number of cases of Crouzon's disease, including some with results that are similar to those the authors noted in their case report. There are, as the authors point out, a number of substantive variables that they have not measured. One variable, which in many ways may be one of the more important, is the hearing acuity of the affected patients and what interventions, either medical, surgical, or rehabilitative, may have been performed to optimize the hearing of each patient. It would be most important, if the authors have this data, if this could be made available.

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Infantile Cholestatic Liver Disease

Sir.—We read with interest the report by Rosenthal et al (JOURNAL 133:1195-1196, 1979) concerning infantile cholestatic liver disease associated with alpha$_1$-antitrypsin deficiency and the Pi-SZ phenotype. We have seen a similar patient who at 1 month of age had failure to thrive and conjugated hyperbilirubinemia. The only other clinical abnormality was a cholesterol level of 415 mg/dL. Rose bengal sodium I 131 did not enter the intestine.

An operative cholangiogram and open biopsy were performed before the results of the alpha$_1$-antitrypsin estimation were known. Bile ducts were present, but some observers thought they were small. Histologically, there was some increase in hepatic ducts and mononuclear infiltration. Diastase-resistant, PAS-positive granules were seen in both hepatocytes and Kupffer's cells. The alpha$_1$-antitrypsin level was estimated to be 90 mg/dL by radial immunodiffusion. The infant's Pi type was SZ, the father's SS, and the mother's MZ. By 2 months of age, the total bilirubin level was 3.3 mg, with the direct at 0.1 mg/dL, and the cholesterol was 292. At 5 months of age he was growing well and the cholesterol level had fallen to 164 mg/dL.

We had been concerned with the specificity of the histological examination of the liver biopsy specimen using PAS and diastase. Sections from a number of patients with jaundice, including galactosemia, unexplained fibrosis, hepatic ductular hypoplasia, and neonatal hyperbilirubi-

nemia were prepared and stained in the same way. All of these patients had normal or elevated levels of alpha$_1$-antitrypsin. We could not detect any difference in the appearance of the PAS-positive granules between any of these samples and that from the infant with the SZ phenotype. We noticed that in published, later biopsy material, the granules are larger and there are clear halos around them. We wonder if other investigators have been similarly confused, particularly in light of the recent report of similar granules in a family with the Dubin-Johnson syndrome.[1]

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1. Lo NS, Chan CW, Hutchison JH: Dubin-Johnson syndrome with some unusual features in a Chinese family. *Arch Dis Child* 54:529-533, 1979.

In Reply.—We are gratified that Drs Harris and Beatty have seen a case that resembles the one reported by us. It was our intent to point out that PAS-positive, diastase-resistant granules may be observed during the first two months in periportal hepatocytes and in Kupffer cells of patients heterozygous for alpha-1-antitrypsin deficiency. As indicated in our article, examination with the electron microscope demonstrated that these deposits were located in the rough endoplasmic reticulum of hepatocytes. In contrast, in patients with cholestasis due to other causes, PAS-positive, diastase-resistant granules may be seen in damaged hepatocytes not usually confined to peripheral regions of lobules, and concentrated in lysosomes rather than in expanded regions of the rough endoplasmic reticulum. The deposits of lipofuscin-melanin pigment observed in Dubin-Johnson syndrome, to which Drs Harris and Beatty refer, are panlobular in distribution and have a dark brown color that may be readily distinguished from the deep red or purple displayed by alpha-1-antitrypsin deposits. Although we are in agreement with Drs Harris and Beatty that the finding of PAS-positive, diastase-resistant granules in hepatocytes is not pathognomonic for alpha-1-antitrypsin deficiency, their presence in a young infant with cholestasis is strongly suggestive, and warrants assessment by determination of serum alpha-1-antitrypsin activity and Pi phenotyping.

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Isosexual Precocity

Sir.—Hung et al in a recent issue of the JOURNAL (134:25-27, 1980) advocated that a computerized tomography (CT) scan be done on any girl or boy with isosexual precocity without an obvious cause or in whom a CNS disorder is suspected. Root has reported that 85% of the cases of isosexual precocity in girls are idiopathic.[1] Eberlein et al studied a series of 86 girls with sexual precocity, and found no cases due to a neurologic disorder.[2] At Charlotte (NC) Memorial Hospital and Medical Center we have seen 77 girls with isosexual precocious development from 1974 through 1979. Only two of these girls had organic pathology—one with an ovarian cyst and one with hydrocephalus (Table). In the cases reported by Hung et al, one girl had hydrocephalus and another had seizures associated with sexual precocity. In both instances, a CT scan was indicated on neurologic considerations alone.

In boys, the incidence of serious pathology is much higher (Table). Root notes that in boys, only 66% of all cases of sexual precocity are idiopathic.[1] The boy in Hung's case had pubertal-sized testes, indicating a central or CNS origin for the precocity. In boys with prepubertal testes and precocity, an adrenal gland disorder would be more common.

Isosexual Precocious Puberty, 1974-1979

	No.
Girls	
Idiopathic	36
Premature thelarche	24
Premature pubarche	15
CNS (hydrocephalus)	1
McCune-Albright disease (ovarian cyst)	1
Boys	
Premature pubarche	6
Adrenogenital syndrome	4
Idiopathic	2
CNS disorder	1

The cost of a CT scan in our institution is $245. The radiation from this procedure is 2 to 10 rads.[3] Although a CT scan may be indicated in selected instances of precocious puberty in girls when a CNS cause is suspected from history or physical examination, we do not think it should be a routine procedure.

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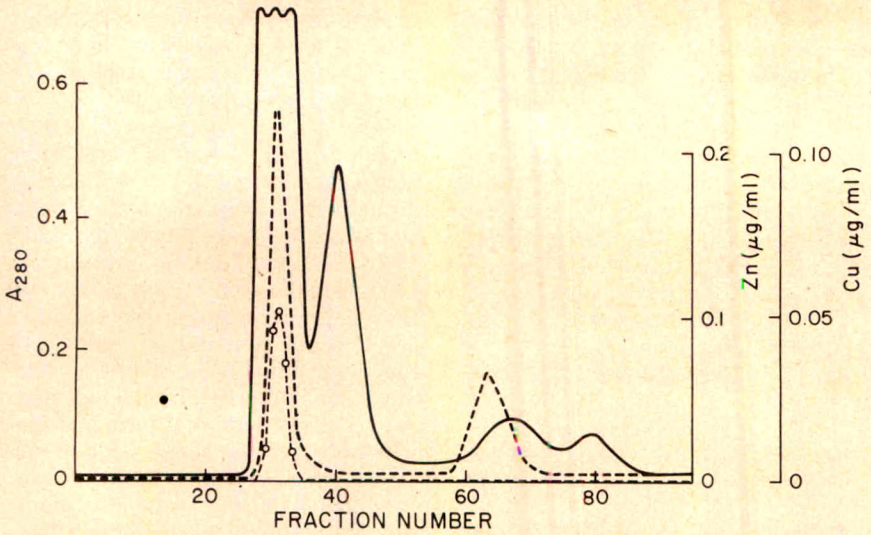
1. Root AW: Endocrinology of puberty: Aberrations of sexual maturation. *J Pediatr* 83:187-200, 1973.
2. Eberlein WR, Bongiovanni AM, Jones IT, et al: Ovarian tumors and cysts associated with sexual precocity. *J Pediatr* 57:484-497, 1960.
3. Bhave DG, Kelsey CA, Burstein J, et al: Scattered radiation doses to infants and children during EMI head scans. *Radiology* 124:379-380, 1977.

Copper Ligands in Human Milk: A Vehicle for Copper Supplementation in the Treatment of Menkes' Disease?

To the Editor.—Recent results from our laboratory have shown that human milk, unlike cow's milk, contains a low-molecular-weight (LMW) zinc complex,[1] now identified as zinc citrate.[2] We have therefore hypothesized that the therapeutic value of human milk in the treatment of acrodermatitis enteropathica (AE), a genetic disorder of zinc metabolism, is due to the presence of this complex, which is thought to be highly available for absorption.[3,4]

Assuming that human milk may contain LMW copper as well as zinc complexes, Williams et al[5] have suggested that human milk may also be of therapeutic value in the treatment of Menkes' kinky hair disease, a sex-linked genetic disorder in humans that is manifested by abnormal intestinal copper absorption and many characteristics similar to those of copper-deficient animals.[6] Despite the aggressive use of copper in infants with Menkes' disease, the prognosis for these patients has not improved.[7] Danks et al[8] have proposed that the primary biochemical lesion in Menkes' disease is the presence of an abnormal protein with a high avidity for copper



Gel filtration of skimmed human milk (2 mL) on a 1.6 × 100-cm fractionating column (Sephadex G-50) in 0.1M ammonium acetate buffer (pH, 6.5). Solid line indicates protein (A_{280}); circles, copper; and broken line, zinc.

and have suggested that treatment of the disease may necessitate the use of a copper chelate which can bypass the mutant protein, making copper available to the cell in concentrations commensurate with both normal cell function and viability. According to the hypothesis of Williams et al,[5] a LMW copper complex (analogous to that found for zinc) that bypasses the intestinal block in Menkes' disease might be found in human milk. These investigators therefore evaluated human milk therapy, but it was not effective. However, we have been studying the molecular localization of copper as well as zinc in human milk and now report that it contains no LMW copper complex.

Methods.—Human milk was obtained from healthy donors through the Mother's Milk Unit, San Jose, Calif. Milk samples were defatted by centrifugation at 10,000 g for 30 minutes. Defatted milk samples were subjected to gel filtration on a (Sephadex G-50) 1.6 × 100-cm fractionating column in 0.1M ammonium acetate buffer at pH 6.5. The gel was treated in sodium borohydride to eliminate small amounts of charges causing nonspecific absorption to the gel matrix.[9] Under these conditions, recovery of copper from the column was 95% to 100%. Absorbance at 280 nm was recorded spectrophotometrically, and copper and zinc in collected fractions as well as in samples were analyzed by flame atomic absorption spectrophotometry.

Results.—The elution profile for human milk on Sephadex G-50 can be seen in the Figure. Copper elutes in a single peak at the elution volume of the column that corresponds to a molecular weight of more than 30,000. No LMW copper complex could be detected. In contrast, zinc elutes in two peaks, one a high molecular weight peak and the second a LMW peak (less than 2,000). Milk samples collected at varying times postpartum showed very similar relative distribution of copper and zinc, and in no case was any LMW copper complex observed.

Comment.—These results demonstrate that in contrast to zinc[2] and iron,[10] there are no LMW copper complexes found in human milk. The lack of such a LMW copper complex may perhaps explain, at least in part, the failure of copper supplementation by milk as a therapeutic treatment for Menkes' disease. These results also provide evidence that the genetic disorders AE and Menkes' disease, although both characterized by abnormal metabolism of a trace element, do not, most likely, produce their effects by similar mechanisms. Thus, while AE can be treated successfully postnatally, it is possible that Menkes' disease requires prenatal treatment. The use of prenatal nutritional manipulation for the prevention or amelioration of deleterious effects of mutant genes has been demonstrated in animal models in the mutant mouse *crinkled*,[11,12] in which there is a disorder of copper metabolism, and in the mutant mouse *pallid*, which has a disorder of manganese metabolism.[13] Likewise, the *screwneck* manifestation in *pastel* mink is prevented by prenatal manganese supplementation.[14] In all three of these cases, only prenatal, and not postnatal, treatment was effective.

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1. Eckhert CD, Sloan M, Duncan J, et al: Zinc binding: A difference between human and bovine milk. *Science* 195:789-790, 1977.
2. Lönnerdal B, Stanislowski AG, Hurley LS: Isolation of a low molecular weight zinc binding ligand from human milk. *J Inorg Biochem* 12:71-78, 1980.
3. Giroux E, Prakash NJ: Influence of zinc-ligand mixtures on serum zinc levels in rats. *J Pharm Sci* 66:391-395, 1977.
4. Hurley LS, Lönnerdal B, Stanislowski AG: Zinc citrate, human milk and acrodermatitis enteropathica. *Lancet* 1:677-678, 1979.
5. Williams DM, Atkin CL, Seay AR, et al: Failure of human milk therapy in Menkes' kinky hair disease. *Am J Dis Child* 133:218-219, 1979.
6. Hurley LS, Keen CL: Teratogenic effects of copper, in Niagru J (ed): *Copper in the Environment*, part 2, *Health Effects*. New York, John Wiley & Sons Inc, 1979, pp 33-56.
7. Garnica AD, Frias JL, Rennert OM: Menkes' kinky hair syndrome: Is it a treatable disorder? *Clin Gen* 11:154-161, 1977.
8. Danks DM, Camakaris J, Stevens BJ: The cellular defect in Menkes' syndrome and in mottled mice, in Kirchgessner M (ed): *Trace Element Metabolism in Man and Animals*. Technische Universität München, Friesing-Weihenstephan, 1978, vol 3, pp 401-404.
9. Lönnerdal B: Chemical modification of dextran gels for gel filtration of trace element ligands. Read before the First International Workshop on Trace Element Analytical Chemistry in Medicine Biology, Neuherberg, Federal Republic of Germany, April 27-29, 1980.
10. Fransson G-B, Lönnerdal B: Iron in human milk. *J Pediatr* 96:380-384, 1980.
11. Hurley LS, Bell LT: Amelioration by copper supplementation of mutant gene effects in the crinkled mouse. *Proc Soc Exp Biol Med* 149:830-834, 1975.
12. Keen CL, Saltman P, Hurley LS: Copper nitrilotriacetate: A potent therapeutic agent in the treatment of a genetic disorder of copper metabolism. *Am J Clin Nutr*, to be published.
13. Erway L, Hurley LS, Fraser A: Neurological defect: Manganese in phenocopy and prevention of a genetic abnormality of inner ear. *Science* 152:1766-1768, 1966.
14. Erway LC, Mitchell SE: Prevention of otolith defect in pastel mink by manganese supplementation. *J Hered* 64:110-119, 1973.

Books

Diseases of the Small Intestine in Childhood, ed 2, by J. Walker-Smith, 412 pp, $49.50, Baltimore, University Park Press, 1979.

This is the second edition of a book first published in 1975. Although the format remains exactly the same, there has been extensive revision of some of the chapters. The author states in the preface that in the four years since his first edition there has been a remarkable expansion of knowledge about diseases of the small intestine. As a consequence, he has felt a need for a new edition to take into account these recent developments. He has succeeded admirably in achieving this goal.

The book contains 12 chapters, which can be divided into three general areas. First is a general introduction, which includes a discussion of history, physical examination, and investigative techniques. The middle section concerns itself with specific diseases, which include coeliac disease, protein intolerance, gastroenteritis, sugar malabsorption, parasites, and Crohn's disease. Finally, there are two chapters on surgical disease of the small bowel. The two areas that have been greatly expanded include the discussions on gastrointestinal viruses and immunology of the gut.

Several chapters are outstanding. Dr Walker-Smith's discussion of small bowel morphology is as well done as any I have seen, but the highlight of the book is the chapter on coeliac disease and dietary protein intolerance. Dr Walker-Smith has a vast clinical experience in these areas, which he beautifully couples to an extensive literature review. The combination results in an unparalleled discussion of the topics. The entire book is well referenced, as evidenced by a 40-page bibliography.

Unfortunately, several weaknesses do exist. The introductory chapter was poorly balanced, with too much space devoted to immunology and not enough to normal intestinal physiology. The chapter on history and physical examination was very superficial and could well have been left out. I also found the chapters on Crohn's disease and massive small-bowel resection rather weak, particularly in the area of management.

These few weaknesses do not come close to offsetting the strengths of the book. Therefore, I recommend this book without reservation for anyone interested in diseases of the small intestine in children.

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Pediatric Neuromuscular Diseases, by Kenneth F. Swaiman and Francis S. Wright, 283 pp, 106 illus, $39.50, St Louis, CV Mosby Co, 1979.

Pediatric Neuromuscular Disease is intended to present a systematic approach to the child with neuromuscular disorders. The first chapter reviews neuromuscular anatomy, history taking and physical examination, normal maturation of the motor system, and central and peripheral hypotonias. The second chapter reviews embryonic development and ultrastructure of muscles and the diagnostic usefulness of electromyography, nerve-conduction studies, and muscle biopsy. Next, the pediatric neuromuscular diseases are classified according to the anatomic location of their chief pathologic conditions. Single chapters are allotted to motor neuron disease, disorders of nerve roots and peripheral nerves, and diseases of the neuromuscular junction. The final three chapters are devoted to muscle disease, discussed under the categories of progressive muscular dystrophies, unusual myopathies and congenital defects of muscle, and myositis.

The detailed clinical descriptions and discussions of differential diagnosis make this a helpful book for the student or clinician in pediatric neuromuscular disease. The more recently described congenital myopathies and metabolic diseases are included, as well as some categories, such as traumatic and vascular neuropathies, that are often omitted from similar texts. The sections on the initial clinical observations and the treatment of Duchenne's muscular dystrophy and of myasthenia gravis are particularly comprehensive and detailed. Good-quality illustrations, including electron micrographs, contribute to the text. Several helpful tables present the differentiating features of the individual disorders within a group of diseases, such as the degenerative anterior horn cell diseases, the neuropathies, the glycogen storage diseases, and periodic paralyses.

Several problems, however, detract from the usefulness of this book as an aid to approaching the child with neuromuscular disease. First, the discussions of pathophysiology of some entities are incomplete. For instance, the discussion of botulism fails to mention the effect of the toxin on release of acetylcholine from nerve terminals. In the description of myotonic dystrophy, no differentiation is made between the congenital form and that with onset in later childhood, and consideration of an intrauterine/maternal factor in the pathogenesis of the congenital form is completely omitted.

Second, organization within the chapters is difficult to follow. This is due in part to the order chosen for presentation of various topics within a chapter. For instance, in chapter 3, benign congenital hypotonia is presented in the middle of the section on degenerative conditions—a misleading representation of its very different prognosis. The unclear chapter organization is also related to the confusing progression of type face chosen to delineate topics and subtopics within the chapters. Subheadings under each disease are in much bolder face than is the disease heading itself. Also, there are inconsistencies in type used for similar headings. For instance, the boldest type to appear in the book is first used to delineate a short section on infectious diseases that cause anterior horn cell disease. Inclusion of the division headings in the "Table of Contents" and at the beginning of each chapter would have been helpful.

Finally, many sections, particularly in the first three chapters, do not read with ease, largely due to redundancy and poor paragraph organization.

Despite these problems, the book's inclusiveness, its up-to-date references, and its detailed clinical descriptions make it a helpful source for students or clinicians caring for children who have neuromuscular disease. For the full-time myologist, it is less helpful than other texts currently available.

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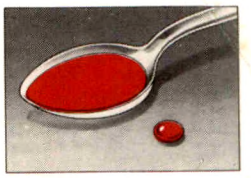

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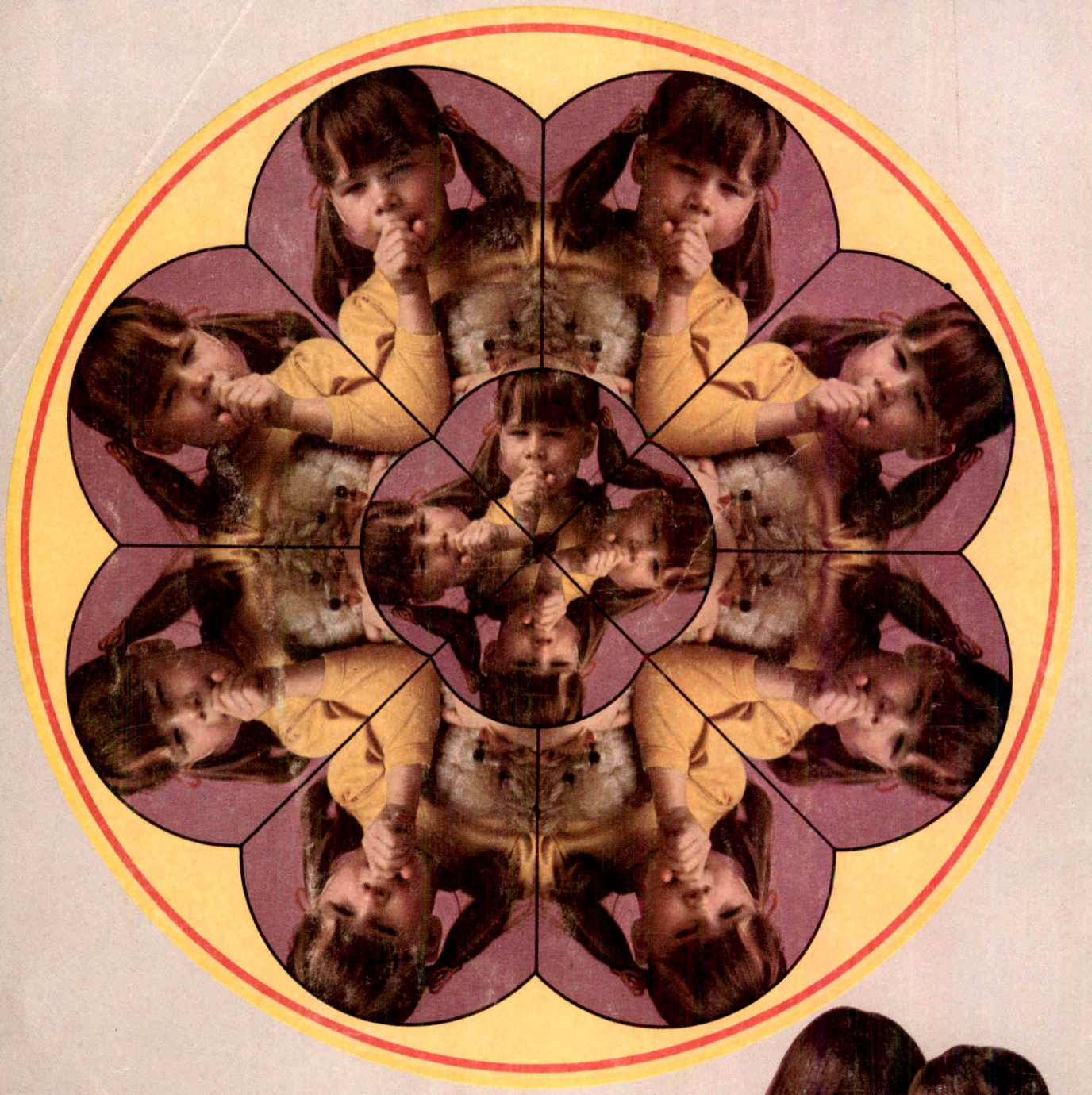

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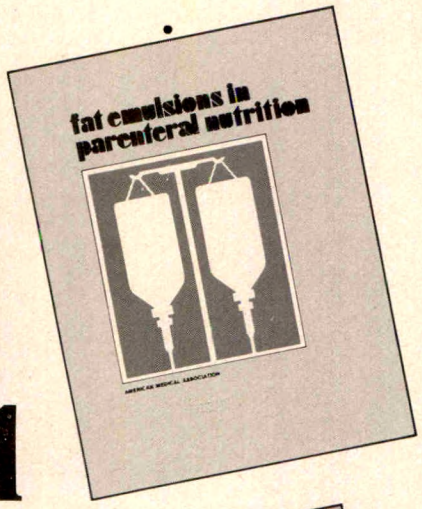

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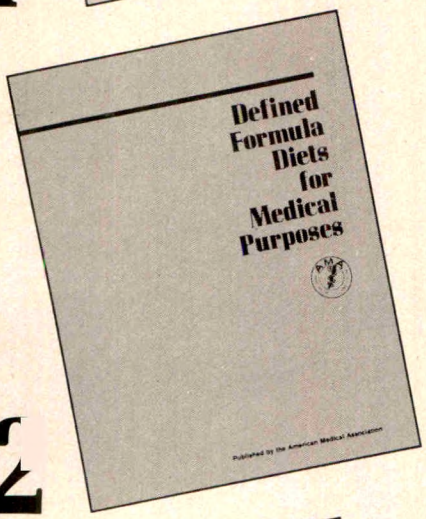

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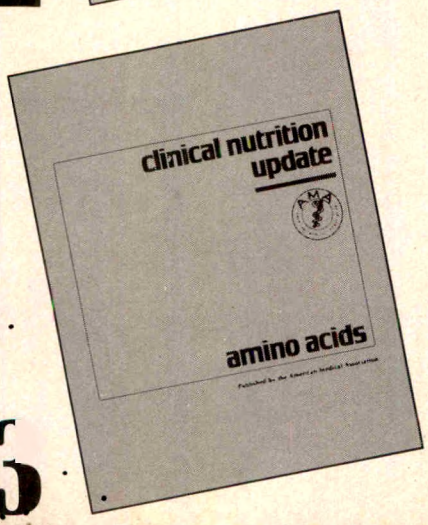

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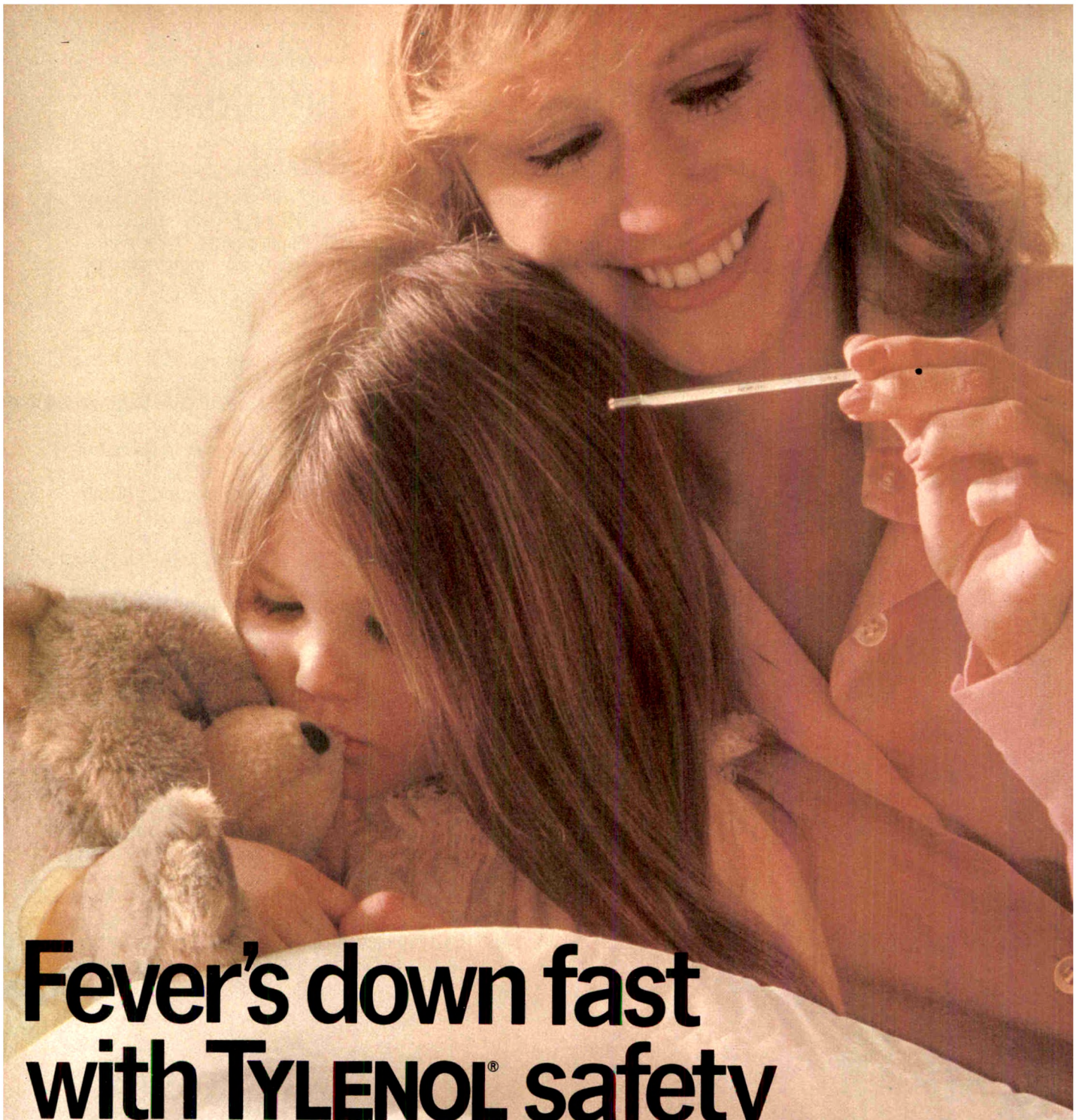

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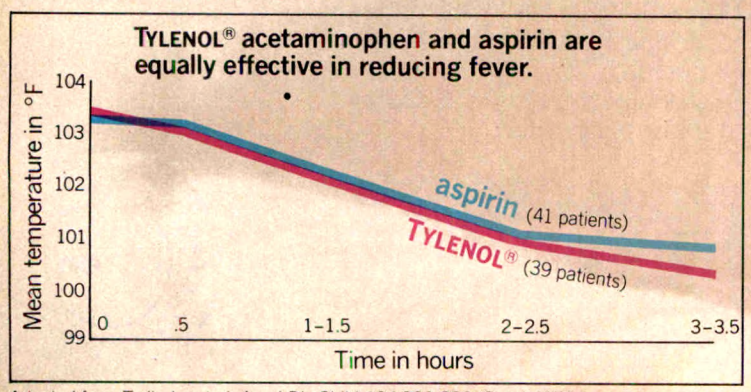

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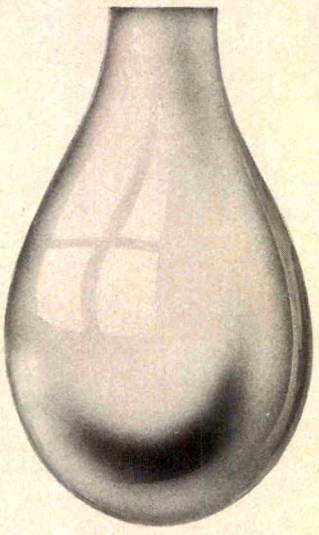

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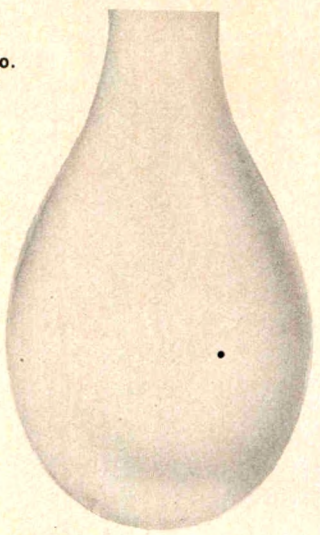

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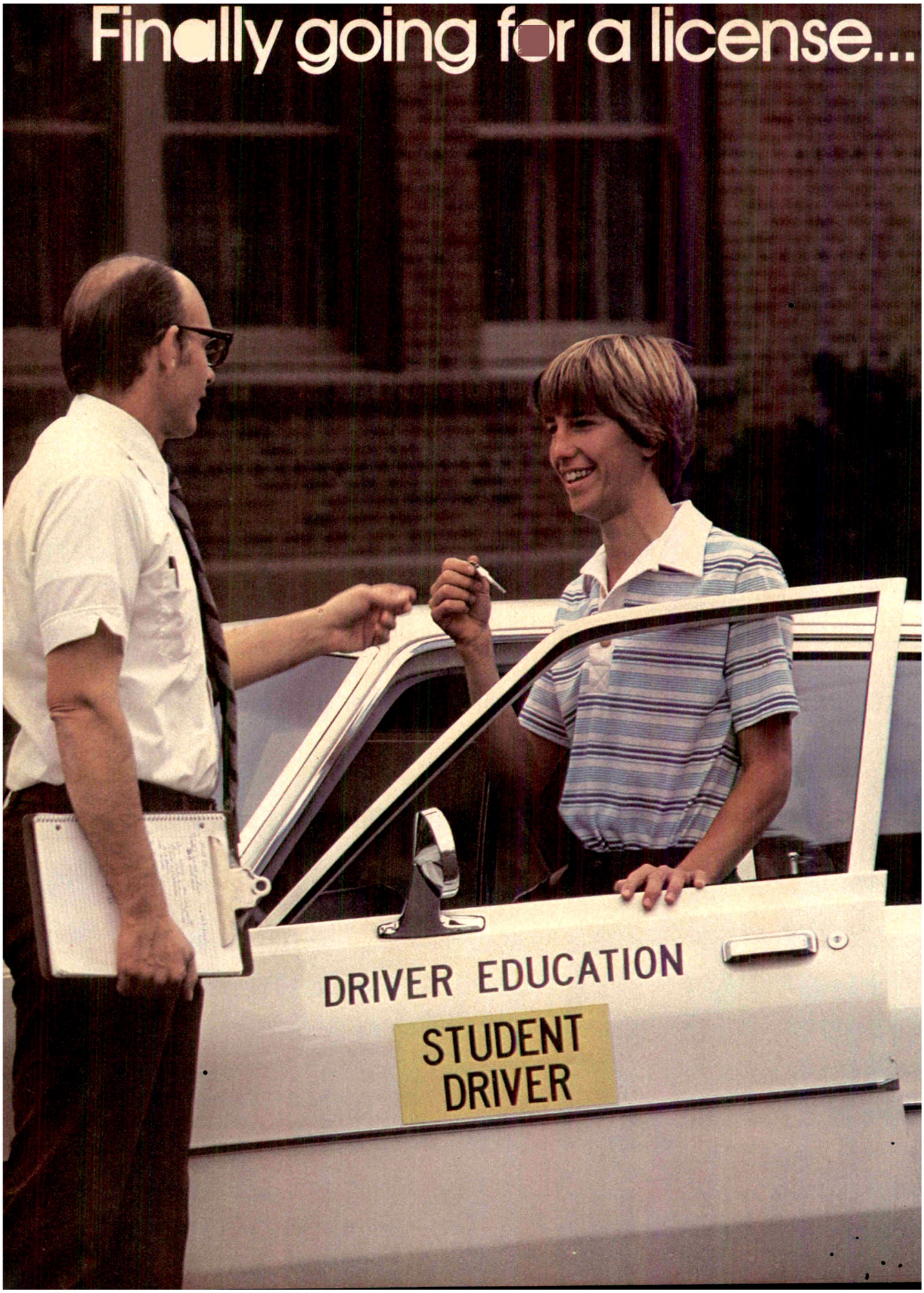
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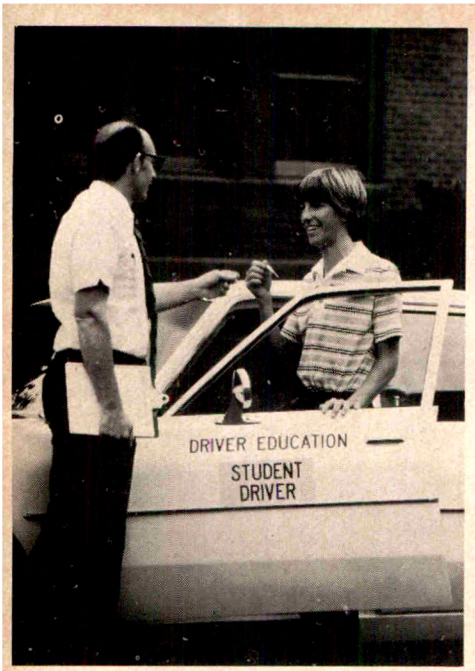
Valproic Acid Capsules 250 mg
250 mg/5 ml syrup



Depakene®
Valproic Acid

Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM OF THE INTERACTION IS UNKNOWN. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY, SERUM BARBITURATE DRUG LEVELS OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF DEPAKENE WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM CONCENTRATIONS. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients also on phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported but do not appear dose related. (See WARNINGS).

OVERDOSAGE: A single case of overdosage with valproic acid has been reported. After ingesting 36 grams in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

Since DEPAKENE is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher doses.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

0018326

ABBOTT

Better than ever, as convenient as ever

Single-Dose Vials

M-M-R® II

MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE (MSD)

Better

contains rubella virus strain RA 27/3

Convenient

one shot vaccinates against all three: measles, mumps, rubella

For a brief summary of prescribing information, please see following page.

MSD
MERCK SHARP & DOHME

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Indications: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Active immunization against measles (rubeola) in children 15 months of age or older.
BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD)—Simultaneous immunization against rubella and mumps in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling.
MERUVAX®II (Rubella Virus Vaccine, Live, MSD)—Immunization against rubella (German measles) in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling. May be useful for adolescent and adult males to prevent or control rubella outbreaks in circumscribed population groups. In postpubertal females vaccination must not be undertaken unless the woman is not pregnant, is susceptible to rubella (as shown by Hemagglutination Inhibition test), agrees not to become pregnant for next three months (also in immediate postpartum period), and is informed of frequent occurrence of self-limited arthralgia and possible arthritis beginning two to four weeks after vaccination.
M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles, mumps, and rubella in children 15 months of age to puberty.
M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD)—Simultaneous immunization against measles (rubeola) and rubella (German measles) in children 15 months of age to puberty.
MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis; therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic and dysgammaglobulinemic states.

Hypersensitivity to Eggs, Chicken, or Chicken Feathers: For measles- and/or mumps-containing vaccines, in patients hypersensitive to eggs, chicken, or chicken feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions.

Pregnancy: *ATTENUVAX*—The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.
Vaccine administration to postpubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of postpubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception that ATTENUVAX, MUMPSVAX, and/or MERUVAX II may be administered simultaneously. BIAVAX II may be administered simultaneously with ATTENUVAX. Monovalent or trivalent poliovirus vaccine, live, oral, may be administered simultaneously with ATTENUVAX and/or MUMPSVAX. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. However, rubella vaccine may be given prior to discharge to susceptible postpartum patients who received blood products, provided that a repeat HI titer is drawn six to eight weeks after vaccination to insure seroconversion; similarly, although rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness, a follow-up postvaccination HI titer should also be determined.
Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines. Vaccination may not result in seroconversion in 100 percent of susceptible subjects.
Measles-Containing Vaccines—Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.
Rubella-Containing Vaccines—Excretion of live attenuated rubella virus from the nose and throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, is not regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.
Measles-Containing Vaccines—Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who previously received killed measles vaccine; the combination vaccines were not given under this condition in clinical trials.
Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5 to 10 cases of SSPE per million cases of natural measles.
Rubella-Containing Vaccines—Adverse reactions include malaise, sore throat, headache, fever, and rash; mild local reactions such as erythema, local pain, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia that is infrequently associated with signs of inflammation, and polyneuritis.
Moderate fever (101–102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.
Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. In children, joint reactions are rare and of brief duration if they do occur. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3 percent; women: 12–20 percent), and the reactions tend to be more marked and of longer duration. Rarely, symptoms may persist for a matter of months. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (35–45 years), these reactions are generally well tolerated and rarely interfere with normal activities.
Mumps-Containing Vaccines—Parotitis and orchitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2–8 C (35.6–46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2–8 C (35.6–46.4 F), and discard if not used within eight hours. Use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.
Color: The color of the vaccine when reconstituted is yellow. ATTENUVAX is acceptable for use only if clear.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)*—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.
BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.
MERUVAX®II (Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than the equivalent of 1,000 $TCID_{50}$ of rubella virus vaccine expressed in terms of the assigned titer of the FDA Reference Rubella Virus, and approximately 25 mcg neomycin.
M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin.
M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles and Rubella Viruses, and approximately 25 mcg neomycin.
MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.
Each of these vaccines is supplied as a single-dose vial with a disposable syringe containing diluent and fitted with a 25-gauge, 5/8" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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MSD
MERCK SHARP & DOHME

Instructions for Authors

General Information.—Send manuscripts by first-class (**not** registered) mail to the Chief Editor, Gilbert B. Forbes, MD, Box 777, 601 Elmwood Ave, Rochester, NY 14642. Designate one author as correspondent and provide his/her address and telephone number. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. Accepted manuscripts become the permanent property of the *American Journal of Diseases of Children* and may not be published elsewhere without permission from the publisher (AMA).

In view of the provisions of *The Copyright Revision Act of 1976*, effective Jan 1, 1978, the author(s) of manuscripts, letters to the editor, and book reviews accepted for publication in the JOURNAL will be required to sign and date the following statement: "In consideration of the AMA taking action in reviewing and editing my/our submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to the AMA in the event that such work is published by the AMA."

Manuscript Preparation.—All the elements of a manuscript must be submitted in **triplicate, double-spaced throughout**. Use heavy-duty white bond paper, 21.6 × 27.9 cm, and 4-cm margins. If a word processor is used, do not justify lines. The style of writing should conform to proper English usage and syntax. All measurements are to be in metric units, temperatures in Centigrade.

All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Titles.—Titles should be short, specific, and clear. They should not exceed 42 characters per line, including punctuation and spaces, and be limited to two lines. The title page should include the full names and academic affiliations of all authors, the address to which requests for reprints should be sent, and, if the manuscript was presented at a meeting, the name of the organization, place, and date on which it was read.

Abstract.—Provide an abstract (135-word maximum) of the article, including statement of the problem, method of study, results, and conclusions. The abstract replaces the summary.

Informed Consent.—Manuscripts reporting the results of experimental investigations on humans must include a statement to the effect that informed consent was obtained from the parents or guardians after the nature of the procedure(s) had been fully explained.

Clinical Memoranda.—Brief accounts of interesting observations and clinical situations. Limited to 800 words plus one table or illustration; abstract unnecessary. Submit in triplicate, double-spaced. Copyright assignment required.

Letters to the Editor.—Correspondence pertaining to material published in the JOURNAL. Limit 500 words. Submit in triplicate, double-spaced, and clearly marked "For publication." Copyright assignment required.

References.—List in order of their appearance in the text, and type double-spaced, in the following manner:

1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 1977; 131:295-296.
2. Koller LR: *Ultraviolet Radiation*, ed 2. New York, John Wiley & Sons, 1965, 141-160.
3. Daughaday WH: The adenohypophysis, in Williams RH (ed): *Textbook of Endocrinology*, ed 5. Philadelphia, WB Saunders, 1974: 31-79.

Do not include unpublished data, personal communications, or manuscripts "in preparation" or "submitted" in the list of references. Such material, if essential, may be incorporated in the body of the article.

Illustrations.—Submit only high-contrast glossy prints in triplicate, unmounted and untrimmed. Preferred size is 12.7 × 17.3 cm (5 × 7 in). Figure number, name of first author, and arrow indicating "top" should be typed on a gummed label and affixed to the back of each illustration. Lettering must be legible after reduction to column size. Magnification and stain should be provided for histologic sections.

For illustrations in full color submit 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies; do not submit color prints. The fee is $275 for up to six square-finished color illustrations that can be arranged on one page. A letter of intent to pay the fee must accompany submission.

Legends.—Legends for illustrations should be typed double-spaced, beginning on a separate sheet of paper (40-word maximum for each).

Acknowledgments.—Illustrations and tables from other publications must be suitably acknowledged, and accompanied by written permission from publisher and author.

Photographic Consents.—A signed statement of consent from **both** parents (or guardian) or the persons involved must accompany all photographs of patients in which a possibility of identification exists. It is not sufficient to cover the eyes to mask identity.

Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 21.6 × 27.9 cm paper. If a table must be continued, use a second sheet and repeat all heads. Each table must have a title.

Uniform Requirements.—Further details on manuscript preparation are given in the document *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* prepared by the International Steering Committee of Medical Editors. Reprints of this document are available by directing requests to this journal: Scientific Publications, 535 N Dearborn St, Chicago, IL 60610.

Increasing resistance of

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor®(cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:
Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).
Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

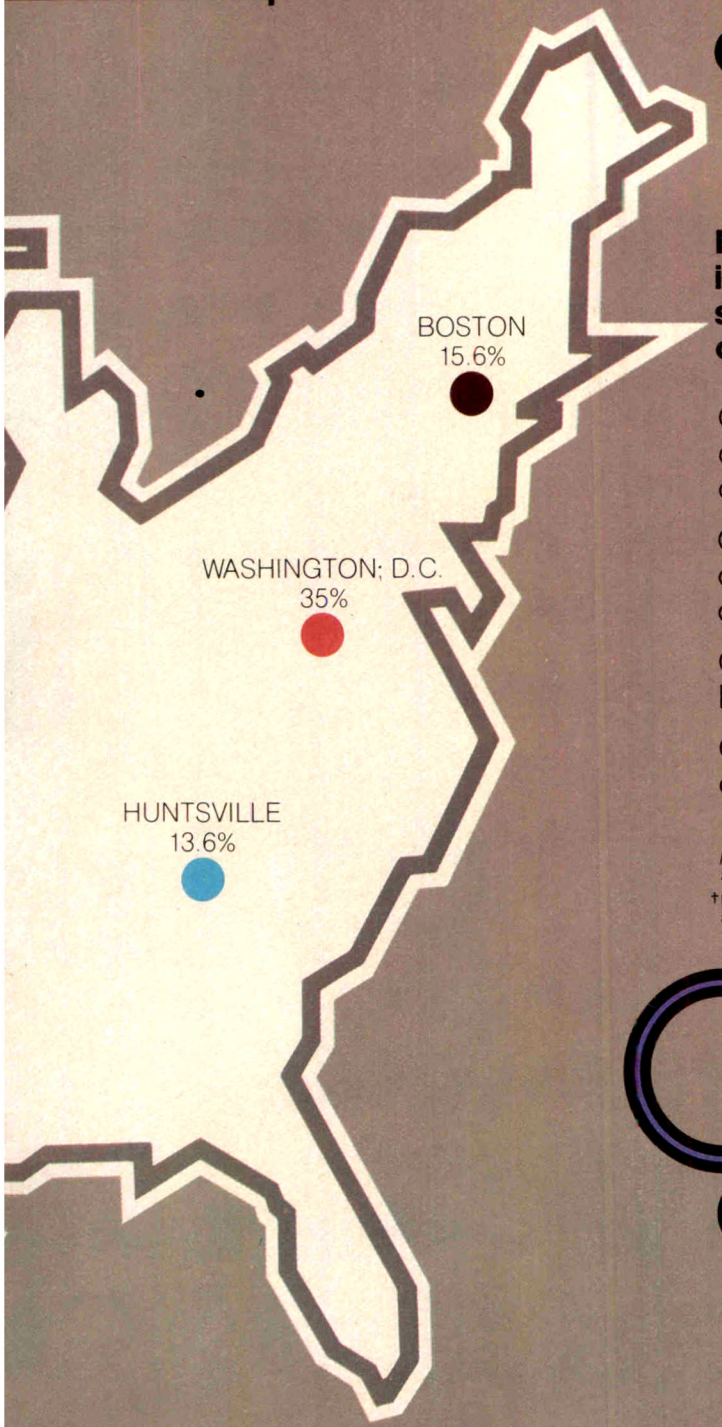
Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).
Antibiotics, including Ceclor® (cefaclor, Lilly), should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.
Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.
Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it

Haemophilus influenzae in otitis media...

a valid concern



In many areas of the country, increasing numbers of *H. influenzae* show resistance to conventional antibiotic therapy.[1-3]

Ceclor is effective in the treatment of otitis media†, including that due to some ampicillin-resistant strains of *H. influenzae*.[4-9]

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Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0703790]

References

1. J. Pediatr., *92*:889, 1978.
2. J. Pediatr., *94*:983, 1979.
3. J.A.M.A., *239*:320, 1978.
4. Antimicrob. Agents Chemother., *11*:470, 1977.
5. Antimicrob. Agents Chemother., *13*:584, 1978.
6. Antimicrob. Agents Chemother., *12*:490, 1977.
7. Current Chemotherapy, *II*:880, 1978.
8. Antimicrob. Agents Chemother., *8*:91, 1979.
9. Antimicrob. Agents Chemother., *13*:861, 1978.
10. Data on file, Eli Lilly and Company.

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Is Propranolol Alone Really Beneficial in Neonatal Thyrotoxicosis?

Bradycardia and Hypoglycemia Evoke the Doctrine of *Primum non Nocere*

In the July issue of the JOURNAL (134:707-708, 1980), Newman et al[1] described an infant with neonatal thyrotoxicosis treated solely with propranolol hydrochloride, which resulted in episodic bradycardia but no improvement in the patient's clinical status. Since this regimen has been recently described as the "treatment of choice" for neonatal thyrotoxicosis, it seems appropriate to call attention to the limitations and possible complications of using only propranolol in this condition.

Smith and Howard[2] seem to have been the first to report the use of propranolol in neonatal thyrotoxicosis, in conjunction with propylthiouracil, Lugol's solution, digitalization, and sedation. These authors recommended that in addition to thyroid blockade, propranolol in a dose of 2 mg/kg be used as standard therapy for the management of neonatal thyrotoxicosis. In the following year, Pemberton et al[3] described an infant with this condition in whom only propranolol was used as therapy; results were apparently satisfactory. Subsequently Pearl and Chambers[4] used only propranolol in a 1,625-g premature infant with neonatal thyrotoxicosis and were favorably impressed.

It is important that those physicians who elect to use β-adrenergic blocking agents in the newborn be familiar with the profound effects these agents are capable of exerting on the fetus, newborn, and child. When propranolol is administered during pregnancy, the infant at birth is at risk for severe depression, manifested by bradycardia and hypoglycemia, both of which are attributable to the β-adrenergic effects of the drug.[5-9] The infant born of a propranolol-treated mother studied by Cottrill et al[7] had no measurable blood glucose at birth; after intravenous 10% dextrose in water the level rose to 15 mg/dL. The infant's plasma propranolol level rose from a value of 42 ng/mL at birth to 90 ng/mL at 4 hours of age. This latter value is comparable to that achieved by the infant of Pemberton et al[3] on propranolol treatment for neonatal thyrotoxicosis (see below). Lieberman et al[8] found that the probability of fetal or neonatal death was significantly higher ($P < .05$) when the mother had been treated with propranolol. Pruyn et al[9] examined ten infants born of mothers who had been on long-term propranolol treatment regimens: three of their babies exhibited hypoglycemia and five had intrauterine growth retardation.

That the older child may also be at risk for hypoglycemia was originally reported by Mackintosh,[10] who described a 9-year-old child receiving propranolol who experienced a grand mal convulsion with a blood glucose value of 12 mg/dL following an overnight fast. The fast was repeated together with propranolol therapy and clinical hypoglycemia again ensued. Similar findings were described by Feller[11] in two propranolol-treated children, the most severely affected of whom was found unconscious and convulsing after fasting overnight, with a blood glucose value of 15 mg/dL.

Hesse and Pedersen described cyanosis, stupor, and pallor in previously healthy siblings (aged 20 months and 3 years) who accidentally ingested 150 mg of propranolol hydrochloride between the two of them.[12] They were not fasting, but the younger had a plasma glucose level of 14 mg/dL and the older a level of 50 mg/dL. They responded promptly to intravenous glucose therapy. Gillette et al[13] administered propranolol to 64 children of varying ages in a study designed to determine the effectiveness of that agent in the management of several cardiac conditions. Ten showed complications of therapy, and treatment was stopped in four cases: two with bradycardia (30 and 50 beats per minute), one with congestive heart failure, and one with somnolence. The infant treated by Pearl and Cham-

bers[4] exhibited vomiting, which is a rare complication of propranolol therapy. Their patient vomited, sometimes in a projectile manner, from the 38th to the 53rd day of life. Vomiting stopped 24 hours after propranolol was discontinued.

Mosier has outlined the contraindications to β-blockade in childhood thyrotoxicosis as follows[14]:

Congestive heart failure that does not respond to digitalis glycosides and diuretics

Atrioventricular block

Obstructive airway disease (including bronchial asthma and allergic rhinitis); (even eyedrops containing the β-blocker timolol, used to treat glaucoma, have provoked severe reactions in patients with bronchial asthma[15] and have aggravated congestive heart failure[16])

Patients taking insulin or oral hypoglycemia agents

Therapeutic failures with propranolol, such as that described by Newman et al in neonatal thyrotoxicosis, have also been noted in adult thyrotoxic patients. Eriksson et al[17] and Jamison and Done[18] have described adults in whom thyroid storm was not prevented by propranolol therapy. Since there may be a wide range of effective propranolol dosage from patient to patient and since neonatal thyrotoxicosis itself varies in severity, the variables faced by the physician in supervising treatment are formidable.

There is an unusual disparity from one study to another in the dosage of propranolol required to achieve a beneficial response, as judged by cardiac and respiratory rates. The two infants described by Smith and Howard[2] required a maximum of 4 to 6 mg/day of propranolol (but they also received propylthiouracil and Lugol's solution). The patient of Pemberton et al[3] received only propranolol, beginning with 2 mg/day at 2 weeks of age and increased according to pulse rate until the baby at 5 weeks was getting 32 mg/day. The latter dosage gave a plasma propranolol concentration of 89 ng/mL two hours after treatment. Pearl and Chambers[4] gave 1.5 mg of propranolol per day beginning at the age of 1 week and increased dosage according to heart rate until at 7 weeks 28 mg/day was being given. In the patient of Newman et al, episodic sinus bradycardia developed at a propranolol dose of only 6 mg/day; clinical improvement did not occur until propylthiouracil and Lugol's solution were added to the treatment regimen and the propranolol was discontinued.

There may be a place for propranolol, along with thionamides and perhaps other medications, in the treatment of neonatal thyrotoxicosis, but there seems little indication for using it alone. The known hazards associated with its use must be weighed against any benefits, and if it is administered, adequate monitoring of the patient for bradycardia, hypoglycemia, and other manifestations of β-blockade must be carried out. Since the relationship of plasma propranolol levels to clinical response and symptomatology is not clear, it would seem important to make such measurements in this rare syndrome.

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Nonproprietary Name and Trademark of Drug

Propranolol hydrochloride—*Inderal.*

References

1. Newman TJ, Virnig NL, Athinarayanan PR: Complications of propranolol use in neonatal thyrotoxicosis. *Am J Dis Child* 134:707-708, 1980.

2. Smith CS, Howard NJ: Propranolol in treatment of neonatal thyrotoxicosis. *J Pediatr* 83:1046-1048, 1973.

3. Pemberton PJ, McConnell B, Shanks RG: Neonatal thyrotoxicosis treated with propranolol. *Arch Dis Child* 49:813-815, 1974.

4. Pearl KN, Chambers TL: Propranolol treatment of thyrotoxicosis in a premature infant. *Br Med J* 2:738, 1977.

5. Gladstone GR, Hordof A, Gersony WM: Propranolol administration during pregnancy: Effects on the fetus. *J Pediatr* 86:962-964, 1975.

6. Habib A, McCarthy JS: Effects on the neonate of propranolol administered during pregnancy. *J Pediatr* 91:808-811, 1977.

7. Cottrill CM, McAllister RG Jr, Gettes L, et al: Propranolol therapy during pregnancy, labor, and delivery: Evidence for transplacental drug transfer and impaired neonatal drug disposition. *J Pediatr* 91:812-814, 1977.

8. Lieberman BA, Stirrat GM, Cohen SL, et al: The possible adverse effects of propranolol on the fetus in pregnancies complicated by severe hypertension. *Br J Obstet Gynaecol* 85:678-683, 1978.

9. Pruyn SC, Phelan JP, Buchanan GC: Long-term propranolol therapy in pregnancy: Maternal and fetal outcome. *Am J Obstet Gynecol* 135:485-489, 1979.

10. Mackintosh TF: Propranolol and hypoglycaemia. *Lancet* 1:104-105, 1967.

11. Feller JM: Danger of hypoglycaemia with use of propranolol. *Med J Aust* 2:92, 1973.

12. Hesse B, Pedersen JT: Hypoglycaemia after propranolol in children. *Acta Med Scand* 193:551-552, 1973.

13. Gillette P, Garson A Jr, Eterovic E, et al: Oral propranolol treatment in infants and children. *J Pediatr* 92:141-144, 1978.

14. Mosier HD Jr: Hyperthyroidism, in Gardner LI (ed): *Endocrine and Genetic Diseases of Childhood and Adolescence.* Philadelphia, WB Saunders Co, 1975, pp 295-317.

15. Jones FL Jr, Ekberg NL: Exacerbation of asthma by timolol. *N Engl J Med* 301:270, 1979.

16. Britman NA: Cardiac effects of topical timolol. *N Engl J Med* 300:566, 1979.

17. Eriksson MA, Rubenfield S, Garben AJ, et al: Propranolol does not prevent thyroid storm. *N Engl J Med* 296:263-265, 1977.

18. Jamison MH, Done HJ: Post-operative thyrotoxic crisis in a patient prepared for thyroidectomy with propranolol. *Br J Clin Pract* 33:82-83, 1979.

Pancuronium and Abnormal Abdominal Roentgenograms

Robert G. Dillard, MD; James E. Crowe, MD; Thomas E. Sumner, MD

• Pancuronium bromide treatment in severely ill, mechanically ventilated infants has been shown to result in lower peak transpulmonary pressures, with an accompanying lower-than-expected incidence of pneumothorax. Infants treated with pancuronium often demonstrate an ominous abdominal roentgenographic finding: the "gasless abdomen." Of 38 mechanically ventilated infants, 22 of 24 pancuronium-treated infants (as compared with four of 14 untreated infants) had diminished or absent bowel gas. There was no significant difference between the two groups with regard to birth weight, mortality, or incidence of respiratory distress syndrome. Pancuronium prevents swallowing of air but does not inhibit gut peristalsis, thus accounting for the evacuation of abdominal gas three hours or more after administration of the drug. Clinicians who treat infants with pancuronium should be aware of the phenomenon, to avoid needless roentgenographic studies.

(*Am J Dis Child* 134:821-823, 1980)

Pancuronium bromide, a neuromuscular blocking agent with little autonomic ganglionic blocking activity,[1] is used to manage neonates who require mechanical ventilation. Treated infants have lower peak transpulmonary pressures and an apparently lower incidence of pneumothorax.[2] With the drug's introduction into our intensive care nursery (ICN), we recognized that its use is often associated with an ominous roentgenographic finding, the "gasless abdomen." In an attempt to analyze the association and to delineate the time course of its occurrence, records and roentgenograms of mechanically ventilated infants in whom pancuronium had and had not been used were reviewed.

SUBJECTS AND METHODS

Medical records and roentgenograms of 83 consecutively ventilated neonates cared for during 1978 in our ICN were reviewed by one of us (R.G.D.). Subjects were selected for study if serial roentgenograms were available that allowed analysis of bowel-gas patterns before, during, and, if the patient survived, after the period of mechanical ventilation. The films for these study infants were reviewed independently by pediatric radiologists (J.E.C. and T.E.S.) without knowledge of the treatment regimen. Roentgenograms were interpreted to have "normal," "borderline," or "diminished" bowel gas.

RESULTS

Thirty-eight of the 83 infants had had roentgenograms that met the criteria. Twenty-four of the 38 infants (63%) had been treated with pancuronium, as compared with 20 of 45 infants (45%) with roentgenograms inadequate for serial evaluation. The difference was not significant ($\chi^2 = 2.18$, $P \geq .1$).

The two radiologists were in complete agreement with regard to their ratings of bowel-gas patterns. Twenty-five infants had films that demonstrated diminished bowel gas, one case was borderline, and 12 infants had normal gas patterns on all films viewed. In analyzing the results, 22 of the 24 pancuronium-treated infants had diminished or borderline patterns,

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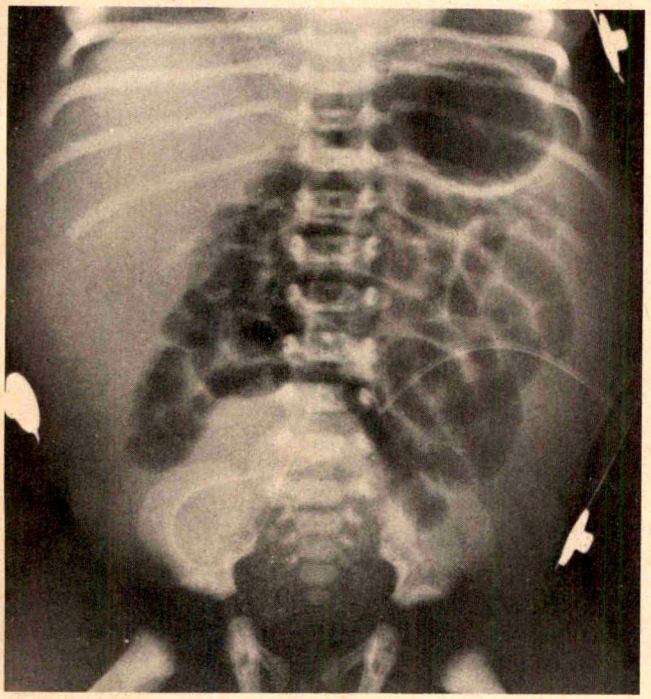

Fig 1.—Roentgenogram taken before administration of pancuronium bromide.

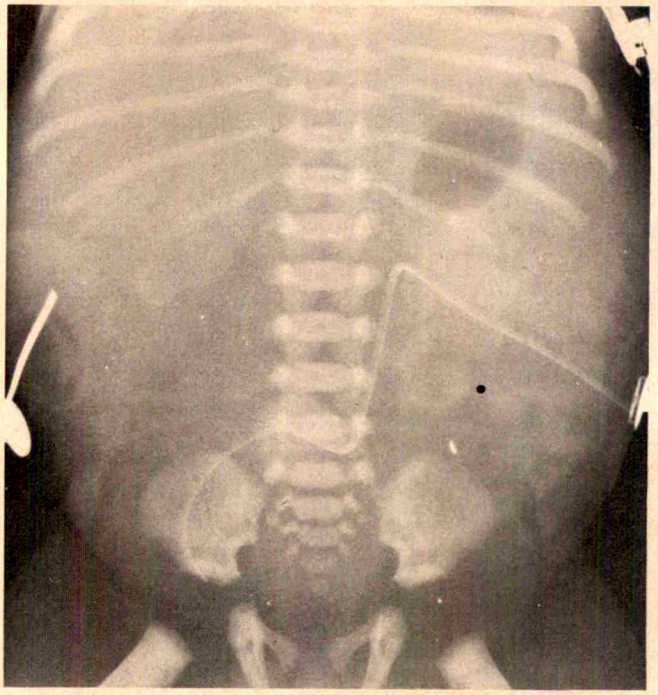

Fig 2.—Roentgenogram taken four hours after administration of pancuronium bromide.

whereas only four of the 14 infants not treated had diminished patterns ($\chi^2 = 19.2$, $P < .001$, Yates' correction).

The treated infants' mean birth weight was 1,923 g (range, 800 to 3,824 g); the untreated group mean was 1,661 g (range, 710 to 3,399 g). The difference was not significant (Kolmogorov-Smirnoff test, $P = .97$). Seventy-one percent of the treated infants died, as compared with 50% of the untreated infants ($\chi^2 = 2.67$, $P > .1$). Seventy-nine percent of the pancuronium-treated infants had the respiratory distress syndrome (RDS), as compared with 71% of the untreated group ($\chi^2 = .306$, $P > .5$). Of the infants with RDS, 69% of the treated infants died as compared with 50% of the untreated infants ($\chi^2 = .94$, $P > .3$).

Of the 22 infants treated with pancuronium and showing diminished gas patterns, seven had roentgenograms taken within two hours of administration of the first dose of the drug. Bowel gas patterns were normal in six of seven. Twenty of the 22 treated infants demonstrated diminished bowel gas patterns on films taken three hours or later after initiation of treatment. The remaining two of the 22 infants had normal gas patterns six hours after administration of the first dose. Subsequent roentgenograms showed absent gas in both.

Figures 1 and 2 are roentgenograms of a representative study infant taken immediately before and four hours after administration of the drug that demonstrate the change in bowel-gas patterns.

REPORT OF CASES

These two cases demonstrate effects of pancuronium on normal and diseased gastrointestinal (GI) tracts.

Case 1.—A 2-kg boy born at 34 weeks' gestation had severe RDS that required mechanical ventilation. His treatment also included administration of pancuronium. On his 5th day of life, while he was still receiving ventilator treatment, a pneumoperitoneum developed. Water-soluble contrast material was instilled into his stomach via a nasogastric tube to rule out a perforated viscus. No perforation was noted and the contrast material passed through the gasless GI tract normally. The pneumoperitoneum was thought to have arisen from a thoracic leak. The patient's course was further complicated by bronchopulmonary dysplasia that required an extended period of mechanical ventilation and supplemental oxygen. He was discharged at 74 days of age.

Case 2.—A 10-day-old, 1.2-kg boy was transferred to our ICN because of abdominal distention. The baby was moribund, with marked increase in abdominal girth. Roentgenograms revealed gaseous distention and multiple areas of pneumatosis intestinalis. Air was present in the portal venous system as well. On the basis of the clinical and roentgenographic findings, a diagnosis of necrotizing enterocolitis was made. Respiratory failure shortly after admission necessitated ventilatory assistance. Pancuronium was used as well. Subsequent abdominal films revealed evacuation of a significant amount of abdominal gas. However, several loops of bowel remained distended and their configuration remained unchanged over three days of conservative medical management. At the time of surgery four days after admission, several segments of gas-filled necrotic bowel were excised. The patient required an extended course of total parenteral nutrition and died as a result of complications of the latter.

COMMENT

Analysis of our data shows a dis-

tinct association between use of pancuronium and diminished or absent bowel gas. Twenty-two of the 24 treated infants, as compared with four of the 14 untreated infants, had abnormal bowel-gas patterns. Siegle has recently described the occurrence of the "gasless abdomen" in two infants treated with pancuronium.[3]

Abdominal films of normal neonates show considerable amounts of bowel gas within three to six hours from birth as a result of air swallowing and effects of gut peristalsis. Infants paralyzed with pancuronium cannot swallow. However, the absence of autonomic ganglionic blockade characteristic of other curare-like drugs permits peristalsis to continue. Any intestinal gas present in the intestines at the onset of drug therapy is evacuated, and without swallowing no further air is introduced.

Although this study did not attempt to confirm this hypothesis as causative of the association, the evidence from case 1 does demonstrate that gut peristalsis is unaffected by pancuronium administration. Contrast material introduced into a previously "gasless abdomen" is evacuated within normal time periods.

Analysis of the time between administration of drug and presence of abnormal gas patterns showed that approximately three hours must pass before evidence of diminished gas appears. Neonates with absent bowel gas on films taken within three hours must be evaluated for other causes of diminished abdominal gas.

Intestinal gas may not be evacuated by pancuronium-treated infants who have abnormal GI tracts. Case 2 illustrates that gas may persist in diseased segments of bowel affected by necrotizing enterocolitis. The infant who persists in having bowel gas three to six hours after administration of adequate amounts of pancuronium should be investigated for the possibility of abnormal gastrointestinal function.

Knowledge of the association between diminished or absent bowel gas and pancuronium use may prevent unnecessary studies of an infant's GI tract. However, it should be remembered that because of the almost universal occurrence of the phenomenon in treated infants, more serious conditions may be overlooked. Likewise, persistent bowel gas in treated infants should be recognized as an abnormal circumstance and investigated accordingly.

Nonproprietary Name and Trademark of Drug

Pancuronium bromide—*Pavulon.*

References

1. Roizen MF, Feeley TW: Pancuronium bromide. *Ann Intern Med* 88:64-68, 1978.
2. Stark AR, Bascom BA, Frantz ID: Muscle relaxation in mechanically ventilated infants. *J Pediatr* 94:439-443, 1979.
3. Siegle RL: Neonatal gasless abdomen: Another cause. *AJR* 133:522-523, 1979.

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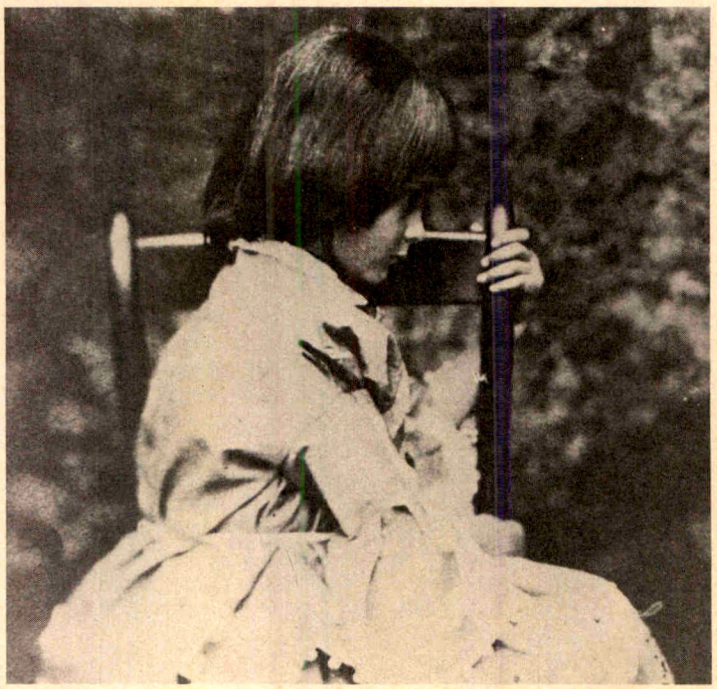

Lewis Carroll (Rev C. L. Dodgson) 1859 From the International Museum of Photography, Rochester, NY
Modern print by A. L. Coburn from negative of original print

Cell-Mediated Immune Defects and Infection

A Study of Malnourished Hospitalized Children

Jean M. Carney, MD; Margaret S. Warner, MD; Thomas Borut, MD; William Byrne, MD; Marvin Ament, MD; James D. Cherry, MD; E. Richard Stiehm, MD

• **Severe protein calorie malnutrition in children in developing countries has been characterized by noticeable depression of cell-mediated immunity and an increased manifestation of infectious illnesses. We studied 23 hospitalized US children whose admitting diagnoses included severe malnutrition to see if similar findings existed. Children were divided into two groups based on the percentage of E rosettes (T cells) prior to nutritional therapy. Those with E rosette values less than 50% were considered to have noticeably abnormal cell-mediated immunity. Eleven of the 23 patients who had rosette values less than 50% had 18 clinical infections, including four episodes of sepsis. One of the 23 children with normal (>50%) E rosettes had one minor infection. It was concluded that depressed cellular immunity as measured by E rosettes is associated with an increased incidence of infectious illness in the malnourished hospitalized pediatric patient in the United States. Other defects in host defenses, ie, defects in complement and phagocytic function, may also have contributed to the increased number of clinical infections noted in these patients.**

(*Am J Dis Child* 134:824-827, 1980)

Children in developing countries with protein calorie malnutrition (PCM) manifest severe and prolonged infectious illnesses.[1] The primary, but not the only, immunologic problem in these children is defective cell-mediated immunity (CMI).[2,3] This defect is characterized by decreased delayed cutaneous hypersensitivity,[4] decreased lymphocyte transformation to phytohemagglutinin (PHA), and low numbers and percentages of T cells.[5] The number of T cells, assessed by their ability to form rosettes with sheep erythrocytes (E rosettes), is a sensitive index of cellular immunity. The degree of E rosette depression generally correlates with the severity of the cellular immune deficit.[6]

Most studies of immune defects in malnutrition have been done on children in developing countries.[7] Recently, investigators have studied malnourished hospitalized adults in this country with PCM.[8-11]

In this report, we assess the relationship between infection and depressed CMI in 23 malnourished hospitalized children in Los Angeles. E rosettes, rather than delayed hypersensitivity skin-test responsiveness were used to evaluate depressed CMI because of known decreased skin-test responsiveness in young normal pediatric patients.[12]

MATERIALS AND METHODS

Patients

All subjects were chosen from the inpatient pediatric service at UCLA hospital and clinics, Los Angeles. All were younger than 18 years of age and had clinical evidence of malnutrition noted in their admission history and on physical examination.

To be included in the study, patients had to have weights less than the fifth percentile for age by National Center for Health Statistics (NCHS) Growth Charts as published in 1976.[13] Weight for height was also obtained from these growth charts.

They were further classified in accordance with the Harvard Standard Weight for Age where 100% of standard is comparable with the 50th percentile on the growth chart.[14] Patients with weight less than 60% of the Harvard standard were judged to have severe PCM and those less than 80% of standard had moderate PCM. Harvard Standard Height for Age was used to estimate the presence of long-term nutritional deprivation. Patients less than 90% of height for age were considered to have chronic severe malnutrition.

The patients' charts were reviewed for age, sex, and admitting diagnosis. Those with illnesses lasting less than one month were described as acute, whereas those with illnesses longer than one-month's duration were considered chronic. Patients with a known primary immunodeficiency diagnosis were excluded. The presence of culture-proved infection and its relation to the time of immune evaluation and the time of nutritional therapy was recorded. Mode of nutritional therapy was also noted, ie, oral feeding, with supplementary peripheral intravenous (IV) feeding or placement of a central venous catheter for total or partial alimentation.

Initial CMI and nutritional assessments were done on all patients before adequate nutritional replacement was begun. Time of adequate nutritional therapy was determined by chart records of steady weight gain and adequate calorie intake.

Cellular immunity was evaluated by E rosettes, absolute lymphocyte count, and PHA stimulation. Humoral immunity was evaluated by quantitative immunoglobulins in some patients. No attempt was made to quantitate possible lymphocyte or immunoglobulin loss from the gastrointestinal (GI) tract. No patients had congenital lymphangectasia to suggest GI loss of lymphocytes. The patients were divided into two groups based on evidence of defective CMI, as measured by E rosettes. Those with E rosette values less than 50% were considered to have evidence of noticeable abnormal CMI (group 1). Those with E rosette values greater than or equal to 50% were considered to have normal or near-normal CMI (group 2). These divisions of rosette values were based on the data of Ferguson et al.[5] Subsequent repeated E rosette determinations were attempted on those patients whose initial values were less than 50%. Laboratory nutritional evaluation for this study was generally limited to complete blood cell count and total serum protein and serum albumin levels; some patients also underwent iron and transferrin studies.

E Rosettes

Heparinized blood was diluted 1:1 with normal saline and mononuclear cells were separated on a Ficoll-Hypaque gradient (sp g, 1.077). The separated cells were washed twice, counted, and adjusted to a concentration of 5×10^6/mL. Fifty microliters of this cell suspension was added to an equal

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Table 1.—Immunologic Studies in Hospitalized Malnourished Children

Immunologic Studies	Normal Values	Group 1: E Rosettes, < 50%			Group 2: E Rosettes, ≥ 50%		
		No. Tested	No. Abnormal	(%)	No. Tested	No. Abnormal	(%)
E rosettes	60%	11	11	(100)	12	0	(0)
Phytohemagglutinin stimulation index	≥ 40	11	5	(45)	11	4	(36)
Absolute lymphocyte count	≥ 2,000 cells/cu mm	11	1	(9)	11	4	(36)
Immunoglobulins	Vary by age						
IgG	. . .	10	7	(70)	5	1	(20)
IgM	. . .	10	9	(90)	5	3	(60)
IgA	. . .	10	9	(90)	5	2	(40)

Table 2.—Infectious Illnesses in Hospitalized Malnourished Children • With Various Degrees of Cellular Immunodeficiency

Infectious Illness	N	Group 1: E Rosettes > 50% (N = 11)	Group 2: E Rosettes < 50% (N = 12)
Shigella dysentary	1*	1*	. . .
Septicemia	5*	5*	. . .
Pyoderma	3	3*	. . .
Pneumonia	2	2	. . .
Superficial candidiasis	2*	1*	1*
Conjunctivitis	2	2	. . .
Urinary tract infection	1*	1*	. . .
Sinusitis	1	1	. . .
Otitis media	1	1	. . .
Bronchiectasis	1*	1*	. . .
Pseudomembranous pharyngitis	1*	1*	. . .
Total	**20**	**19†**	**1**

*Infection documented by bacterial or fungal culture.
†Total is more than number of patients in group because several patients had more than one infection.

volume of a sheep's RBC (S-RBC) suspension (5.0×10^7 cell/mL) in heat inactivated (S-RBC) absorbed human AB serum. The mixture was centrifuged at 150 g for five minutes and incubated overnight at 4 °C. Cells were gently resuspended and the number of lymphocytes binding at least three or more S-RBCs were counted. Duplicate samples were run on each specimen, with a normal young adult control included each day (E rosette percentages of young adult controls in this laboratory do not differ significantly from normal pediatric controls). Results were expressed as percent of lymphocytes forming rosettes and as an absolute number in some patients, based on total lymphocyte count. A total lymphocyte number would normally be greater than 2,000, and 60% would be the normal percent of T cells, so a count greater than 1,200 would be a normal number of T cells.

PHA Stimulation

Mononuclear cells were resuspended at a concentration of 1.0×10^6 cells/mL in asynthetic liquid tissue culture media developed at Roswell Park Memorial Institute (RPMI 1640) with 20% heat-inactivated human AB serum. One hundred microliters of the cell suspension was incubated in tissue culture plates in triplicate with three dilutions of PHA and without PHA in a humidified 5% CO_2 37 °C incubator for 72 hours.

Two microcuries of tritiated thymidine was added to each culture and cultures were harvested 18 hours later onto glass fiber-filter disks, then dried and counted in a scintillation counter. Results were expressed as an index or ratio of the highest counts of the stimulated cells to the unstimulated cells. A stimulation index of less than 40 was considered abnormal. Normal control samples were run daily.

Quantitative Immunoglobulins

Quantitative immunoglobulins were performed using radioimmunodiffusion. Because normal values vary for different-aged children, results were evaluated as normal, increased, or decreased more than 1 SD from normal for age.

Nutritional Studies

Nutritional studies were done by the UCLA Hospital Clinical Laboratory. Laboratory normal values for these studies were as follows: albumin, >3.2 g/dL; total protein, >6 g/dL; serum iron, >50 μg/dL, serum transferrin, >280 μg/dL; and hemoglobin, >10 g/dL.

RESULTS
Clinical Evaluation

Twenty-three patients were examined; all were less than the fifth percentile weight for age on NCHS growth charts. When evaluated by the Harvard Standard Weight for Age, 16 (69%) of the children were 60% to 80% of the standard and the other seven (31%) were less than 60% of the standard, characteristic of moderate to severe PCM. Sixteen of the children had heights less than 90% of the Harvard Standard Height for Age, characteristic of long-standing nutritional deprivation. Eighteen patients (78%) were less than the fifth percentile weight for height and five (12%) were at or below the 25th percentile of the NCHS growth charts.

Fifteen patients were boys and eight were girls. Twelve were less than 1 year of age and 11 were 1 to 18 years of age. Admitting diagnoses were primary GI disease (11 patients) or miscellaneous other conditions (12 patients). The latter included starvation in three Vietnamese refugee infants and severe failure-to-thrive in one infant secondary to maternal neglect. Three others had chronic pulmonary disease, asthma, cystic fibrosis, and interstitial fibrosis. Two had anorexia nervosa. One patient had granulocytopenia that resolved spontaneously and one was hyperthyroid. Twenty-two of the 23 patients had illnesses of greater than one month's duration, nine patients required placement of a central venous catheter, whereas 14 required only peripheral IV and oral alimentation.

When patients were grouped according to CMI as measured by E rosettes, there were no significant differences between those children in group 1 and group 2 in weight for age, height for age, or weight for height.

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The mean age was 3.48 years for group 1 and 5.42 years for group 2. Five patients in group 1 and seven patients in group 2 were 12 months old or younger. Four children with normal or only slightly abnormal E rosette values required central vein lines and five of those with noticeably abnormal E rosette values received central alimentation.

Immune Evaluation

Immune studies were performed usually within 48 to 72 hours of admission, which would have been during the time of an infectious illness in eight patients in group 1. In three patients in whom clinical infections developed while they were in the hospital, the immune studies were performed prior to the clinical manifestations. In the one child who had multiple episodes of septicemia, the immune studies were done between the third and fourth septic episodes. No infections were associated with the central feeding catheters.

Immunologic studies in group 1 and group 2 patients are compared in Table 1. By definition, E rosette evaluation was done on all 23 children since subsequent grouping of CMI was based on these values. The mean E rosette value of group 1 was 40 compared with 63 in group 2. Eight patients from group 1 were reexamined ten to 14 days later and their rosette percentages had returned to a normal range. Two children in this group were reexamined three and six months later and normal E rosette percentages were observed. The means of the absolute number of T lymphocytes calculated from seven of 11 patients in group 1 and seven of 12 patients in group 2 were 1,502/cu mm and 2,773/cu mm, respectively. EA rosettes, a measurement of B cells by presence of crystallizable fragment (Fc) receptors, were available on eight patients in group 1 and nine in group 2. There were no differences between the two groups in either numbers or percentages of EA rosettes. Indices of PHA stimulation were obtained on 22 patients. Depressed PHA values were seen in nine patients, five of 11 in group 1 and four of 11 examined in group 2. However, the mean PHA index for the two groups was not significantly different. The mean absolute lymphocyte count was 4,655/cu mm in group 1 children and 4,907/cu mm in group 2 patients, with five individual values between 1,500 and 2,000/cu mm.

No children had diminished immunoglobulin levels. Increased IgG levels were noted in the serum of seven of ten in group 1 but in only one of four examined in group 2. Levels of IgM were increased in nine of ten in group 1 and in three of five in group 2. Levels of IgA were also increased in nine of ten in group 1 and in only two of five in group 2. These findings suggest an increased humoral immune stimulation in patients in group 1 compared with those in group 2.

Infectious Illnesses

Culture-documented clinical infections and presumed bacterial or fungal infections are given in Table 2. In group 1, those with noticeably abnormal E rosette values, 19 clinical infections occurred in 11 patients; none was free from evident infection. Eight patients in this group had clinical infections at the time of their hospital admission; clinical infections developed in three while they were hospitalized. This included a 2-month-old boy with a staphylococcal pseudomembrane in the posterior pharynx and possible sepsis in whom granulocytopenia developed shortly after admission and he did not respond to antibiotic therapy. Improvement in his clinical status was temporally related to placement of a central alimentation line and granulocyte transfusion. The granulocytopenia resolved spontaneously and did not recur.

An *Escherichia coli* urinary tract infection and *Enterobacter cloacae* septicemia occurred in a 2½-month-old boy with chronic diarrhea five days after admission. His condition improved with antibiotic therapy and adequate nutrition via a central line.

A 4-month-old boy had four episodes of sepsis during a lengthy hospitalization. This child had GI malabsorption that did not improve with multiple different feeding regimens. The patient had been hospitalized for 3½ months, had had three episodes of sepsis, but still had not had substantial weight gain at the time of this evaluation. Only after a central alimentation line was placed for total parenteral nutrition did weight gain occur and septic episodes cease. He had a history of recurrent hematest-positive stools with oral feedings. This could indicate increased gut permeability and susceptibility to infection that also would have improved with the no oral feeding regimen.

Only one patient in group 1 had considerable problems with infections after nutritional replacement. This patient was a malnourished 13½-year-old girl with cystic fibrosis who had been hospitalized every two months for increased pulmonary infection during the preceding ten-month period. With the placement of the central feeding catheter and doubling of her daily caloric intake, she gained weight and was not hospitalized again for 12 months. Her central feeding catheter was also used for intravenous antibiotic therapy that certainly could have contributed to her year-long clinical improvement. She subsequently died of pneumonia, presumably due to an influenza A viral infection.

Of the patients with slightly depressed or normal cellular immunity (group 2), only one had a clinical infection, a *Candida* diaper rash. None of the others in this group had an infectious illness on admission nor did clinical infection subsequently develop during hospitalization. When those patients who had placement of a central venous line were examined separately, none had episodes of sepsis or local infection that could be related to the IV catheter.

Nutritional Studies

Five of 21 children tested had a low serum albumin level and six of 21 had low total protein levels. Seven of 23 had low hemoglobin levels, nine of 14 had low serum iron levels, and six of 12 had low transferrin levels. Mean values for albumin, total protein, and hemoglobin levels were not low in either group 1 or 2. Mean serum iron and transferrin values were low in the whole study population but without a significant difference between groups 1 and 2.

COMMENT

Our findings document the presence of severe and moderately severe malnutrition in a hospitalized pediatric population, although the actual extent of malnutrition was not determined in this study. In a survey of a general adult medical ward,[15] 54% of the patients had moderate to severe mal-

nutrition based on clinical and anthropometric evaluation. A similar study would be appropriate in a pediatric facility.

The at-risk pediatric population for malnutrition in this study seemed to be a group of younger chronically ill children, with long-standing disease, as evidenced by half of the patients being younger than 1 year of age and less than 90% height/age. This younger-aged population also seems to be at higher risk for serious infections in association with malnutrition, since all episodes of septicemia were observed in these children.

Coexistence of severe malnutrition with an increased prevalence of clinical infection has been previously noted by many investigators.[1,2] The use of E rosettes as a sensitive indicator of depressed CMI in pediatric patients has been reported by Ferguson et al[5] and a decreased percentage of E rosettes was associated with an increased incidence of clinical infections in their study of Ghanian children. In this present study, as in the study by Ferguson et al, the decreased percent of E rosettes did not always correlate with severity of infection but only with the presence of some type of infectious illness. Anthropomorphic measurements and biochemical and hematologic abnormalities associated with malnutrition did not correlate with the presence of clinical infection and low rosette valnor did they in previous investigations.

In this patient population, the percentage of E rosettes was decreased and the absolute number of lymphocytes was decreased. It is difficult to determine whether the decreased T-lymphocyte values were the result of infections or were evidence of increased susceptibility to infectious illness because most patients had both when their conditions were initially evaluated. However, serious bacterial infections subsequently developed in three patients with no evidence of clinical infection and low rosette values when first seen. One might speculate that the infections occurred in these patients because of lack of T cells, as they have a role in antigen processing for specific immunoglobulin production. This does not rule out the presence of other immune defects in severe malnutrition (ie, in the complement system and phagocytic cells) that would also contribute to increased infection. However, these aspects of immunity were not examined in this patient group. Since there is known depression of cellular immunity after many viral infections, it would have been helpful to confirm the presence or absence of a preceding viral infection in these patients. Unfortunately, this possibility was not considered at the time.

Values for PHA, although decreased in nine (41%) of the patients examined, were not different in the two groups. Indices of PHA stimulation have been reported to be decreased in severely malnourished patients, although not consistently. The presence of this abnormal finding in slightly less than half of our patients may reflect small sample size. It may also indicate that PHA indices are not as sensitive an indicator of depressed cell-mediated immunity in pediatric patients as are E rosettes. The PHA indices did not correlate with the presence of clinical infection in this population.

The elevated immunoglobulin levels, particularly IgA and IgM in group 1 patients may reflect response to infection in some patients or a loss of some suppressor control of immunoglobulin synthesis associated with decreased cellular immunity. Absolute lymphopenia occurred in 21% of our patients; Ferguson et al[5] had reported 5% and Smythe and associates[3] reported 27% in their pediatric patients with severe malnutrition. Lymphopenia did not correlate with depressed E rosettes or with presence of clinical infection.

The association of decreased E rosette levels with malnutrition and infection does not seem to occur in malnourished adult hospitalized patients. Bistrian et al[9,10] reported hospitalized adults with marasmus and PCM who had normal in vitro tests of CMI, including absolute lymphocyte counts, E rosettes, and lymphocyte transformation to PHA, concanavalin, and other mitogens and antigens. Law et al[8] showed a depressed response to PHA and pokeweed mitogen in malnourished adults as compared with controls, but they did not evaluate E rosettes.

We consider the depression of E rosette levels as one possible indicator of increased susceptibility to clinical infection in malnourished children. This should be examined further by studying a larger group of malnourished hospitalized pediatric patients, and correlating both E rosettes and delayed hypersensitivity skin-test responses with prevalence of infections. Other variables of the immune system, ie, complement system and phagocytosis, need to be evaluated in this population as well.

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References

1. Scrimshaw NS, Taylor CE, Gordon JE: *Interactions of Nutrition and Infection*. World Health Organization Monograph Series No. 57, WHO, Geneva, 1968.

2. Neumann CG, Lawlor GJ, Stiehm ER, et al: Immunologic responses in malnourished children. *Am J Clin Nutr* 28:89-104, 1975.

3. Smythe PM, Schonland M, Brereton-Stiles GG, et al: Thymolymphatic deficiency and depression of cell-mediated immunity in protein-calorie malnutrition. *Lancet* 2:939-943, 1971.

4. Edelman R, Suskind R, Olson RE, et al: Mechanisms of defective delayed cutaneous hypersensitivity in children with protein-calorie malnutrition. *Lancet* 1:506-508, 1973.

5. Ferguson AC, Lawlor GJ, Neumann CG, et al: Decreased rosette-forming lymphocytes in malnutrition and intrauterine growth retardation. *J Pediatr* 85:717-723, 1974.

6. Seeger RC, Stiehm ER: T and B lymphocyte subpopulations. *Pediatrics* 55:157-160, 1975.

7. Suskind RM (ed): *Malnutrition and the Immune Response*. New York, Raven Press Inc, 1977.

8. Law DK, Dudrick SJ, Abdou NI: Immunocompetence of patients with protein-calorie malnutrition: The effects of nutritional repletion. *Ann Int Med* 79:545-550, 1973.

9. Bistrian BR, Blackburn GL, Scrimshaw NS, et al: Cellular immunity in semistarved states in hospitalized adults. *Am J Clin Nutr* 28:1148-1155, 1975.

10. Bistrian BR, Sherman M, Blackburn GL, et al: Cellular immunity in adult marasmus. *Arch Intern Med* 137:1408-1411, 1977.

11. Pietsch JB, Meakins JL, MacLean LD: The delayed hypersensitivity response: Application in clinical surgery. *Surgery* 82:349-355, 1977.

12. Stiehm ER, Neumann CG, Swendseid ME, et al: Humoral and cellular aspects of immunity in malnutrition: XII. Symposium of the Swedish Nutritional Foundation, in Hambraeys L, Hanson LA, McFarlane H (eds): *Food and Immunology—Proceedings of a Symposium of the Swedish Medical Research Council*. Stockholm, Almqvist & Wiksell International, 1977, pp 69-85.

13. *National Center for Health Statistics Growth Charts, 1976 Monthly Vital Statistics Report*, vol 25, No. 3, suppl (HRA). Rockville, Md, Health Resources Administration, 1976, p 76.

14. Jelliffe DB: The assessment of the nutritional status of the community. *WHO Monogr Ser* 53:221, 1966.

15. Bistrian BR, Blackburn GL, Vitale J, et al: Prevalence of malnutrition in general medical patients. *JAMA* 235:1567, 1976.

'Normal' Technetium Bone Scans in Patients With Acute Osteomyelitis

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• **Several investigators have stressed the usefulness of the technetium bone scan in the early diagnosis of acute osteomyelitis. Seven patients with acute osteomyelitis had initial bone scans that were reportedly normal. The diagnosis was made as a result of either an abnormal gallium scan, positive cultures, or changes in follow-up roentgenograms. The explanation for the normal technetium scans is conjectural but may be related to compromised vascularity. A normal scan does not rule out acute osteomyelitis. If this diagnosis is strongly suspected, other diagnostic tests should be used.**

***(Am J Dis Child* 134:828-830, 1980)**

Numerous reports in recent years have emphasized the usefulness of technetium bone scintigraphy in the early diagnosis and localization of acute osteomyelitis, as well as the disease's differentiation from cellulitis, bone infarction, and septic arthritis.[1-5] Some authors have even expressed the opinion that a normal scan rules out acute osteomyelitis.[2-4] This report, which describes the occurrence of falsely normal technetium scans in patients with acute osteomyelitis, is prompted by our recent experience in managing several patients with this disease in whom normal bone scans were reported.

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SUBJECTS AND METHODS

The patients described were hospitalized at either the Children's Hospital of Denver, the University of Colorado Medical Center, Denver, or Denver General Hospital during the years 1975 to 1979. Roentgenograms and technetium bone scans were performed within 48 hours of admission because of the clinical suspicion of acute osteomyelitis. Gallium scans of some patients were obtained later in the hospitalization because of persistent symptoms and signs consistent with the diagnosis of acute osteomyelitis in spite of reportedly normal roentgenograms and technetium bone scans. Repeated roentgenograms of most patients were obtained eight to 16 days after the onset of symptoms. The technetium Tc 99m medronate (Methylene Diphosphonate [Sn] Kit) and gallium citrate Ga 67 scans were performed using standard methods and doses. Localized vascular-flow studies were routinely done on patients examined for possible osteomyelitis. Multiple angle scintigrams were performed after a two-hour delay using a standard 37-tube Anger camera or a linear multiplane emission computerized tomographic unit. Gallium scan images were obtained in the same manner after a 48-hour delay using the same equipment. Criteria for the diagnosis of acute osteomyelitis included a consistent clinical presentation together with either (*a*) focal uptake of gallium citrate Ga 67 by the affected bone; (*b*) subsequent roentgenographic evidence of bone destruction or periosteal reaction; or (*c*) aspiration of pus from affected bone.

RESULTS

The cases of seven patients with acute osteomyelitis are described. A summary of the patients' ages, the sites of lesions, and the roentgenographic, scintigraphic, and microbiologic findings is given in the Table. The ages of the patients ranged from 3 weeks to 8 years. The technetium Tc 99m medronate bone scan in each of the cases was reported as showing no focal uptake by bone (Figure). The technetium scans were performed three to five days, and the gallium scans seven to eight days, after the onset of symptoms. The diagnosis of acute osteomyelitis was confirmed by subsequent roentgenographic changes in four patients, by an abnormal gallium scan and positive culture in one patient, and by an abnormal gallium

scan alone in two patients. Repeated technetium scans were not performed. All patients recovered with appropriate antibiotic management.

COMMENT

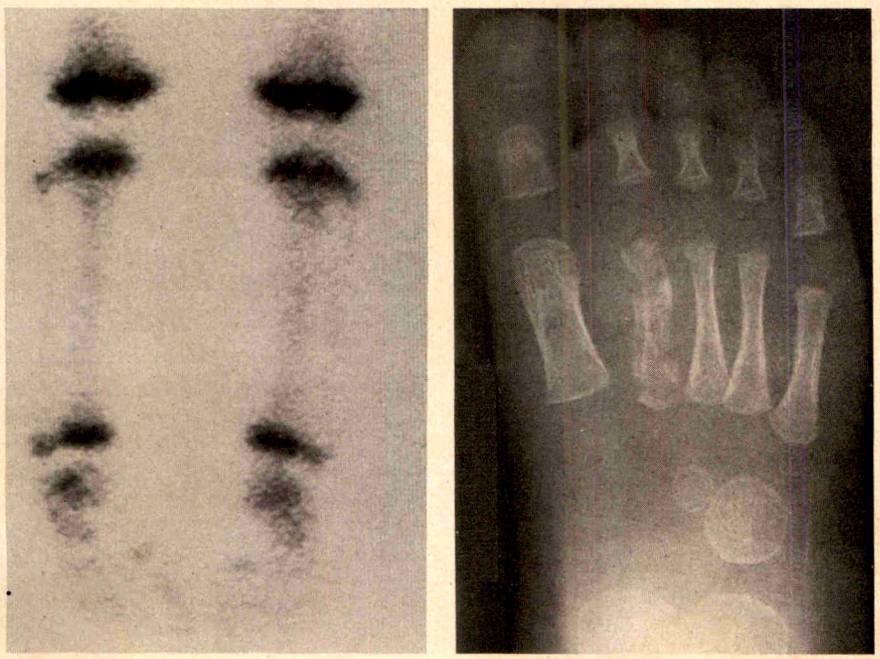
In spite of the reports emphasizing the usefulness and sensitivity of technetium Tc 99m medronate bone scintigraphy in confirming the diagnosis of acute osteomyelitis as early as 24 to 48 hours after the onset of clinical symptoms,[2,3] the cases herein reported demonstrate that the disease can be present despite a normal or equivocally abnormal bone scan. With the exception of the case reported by Garnett et al[6] and rare mention of a falsely normal scan in some series,[2,3] this phenomenon has not been, to our knowledge, previously emphasized.

An explanation for this finding is conjectural. Evidence suggests that the accumulation of technetium Tc 99m medronate by bone is dependent on ionic exchange, the phosphate moiety of the technetium phosphate complex exchanging with phosphate on the hydroxyapatite crystal surface. This exchange will occur at an

Roentgenographic, Scintigraphic, and Microbiologic Findings After Onset of Symptoms in Patients With Acute Osteomyelitis

	Roentgenography: Days, Result		Scintigraphy: Days, Result		
Case/Age/Sex	Initial	Follow-up	Technetium Tc 99m Medronate	Gallium Citrate Ga 67	Microbiologic Results
1/3 yr/M	4, soft-tissue swelling	18, normal	5, normal	7, focal increased uptake metaphysis, L distal femur	Blood, sterile; needle aspirate subperiosteum, sterile
2/6 yr/M	3, normal	15, normal	4, normal	7, focal increased uptake, L proximal femoral metaphysis	Blood, sterile; hip joint, sterile; needle aspirate proximal femoral metaphysis, sterile
3/3 wk/M	3, soft-tissue swelling	. . .	6, normal	8, focal increased uptake, L distal femoral metaphysis	Blood, sterile; needle aspirate distal femoral metaphysis, group B β-hemolytic streptococcus
4/1½ yr/M	2, soft-tissue swelling	7, osteolytic lesion, second metatarsal	3, normal	. . .	Blood, sterile; needle aspirate distal second metatarsal, sterile
5/1½ yr/M	4, soft-tissue swelling	11, osteolytic lesion, L proximal tibial metaphysis	4, normal*	. . .	Blood, *Staphylococcus aureus*
6/8 yr/M	4, normal	12, osteolytic lesion, R ischium	5, normal*	7, focal increased uptake, R ischium	Blood, *S aureus*
7/2½ yr/F	2, normal	4, periosteal reaction, proximal shaft R femur	3, normal*	7, focal increased uptake, proximal shaft R femur	Blood, sterile; hip joint, sterile

*Equivocally abnormal on retrospective review.



Left, Normal technetium Tc 99m medronate scan, case 4. Right, Roentgenogram 18 days after onset of symptoms, showing osteolytic lesions in second right metatarsal, case 4.

increased rate in all areas of accelerated bone turnover whether this increased activity is normal, eg, epiphyseal centers in children, or pathologic, eg, osteomyelitis or fractures.[4-7] This localization of isotope is also facilitated by the increase in bone vascularity that frequently accompanies bone infection.

The vascular factors involved in pathogenesis of acute osteomyelitis have been reviewed by Waldvogel et al.[8] Infection within the metaphysis with intraosseous pus accumulation, sinusoidal thrombosis, venous thrombophlebitis, and possible subperiosteal abscess compression of the nutrient arteries can produce areas of metaphyseal ischemia. The net effect of focal ischemia, offset by the increased extraction of radionuclide associated with osteoblastic proliferation, may explain the occasional normal bone scan. There are, in fact, reports of cases of acute osteomyelitis in which "cold" lesions on bone scan have provided scintigraphic evidence of focal bone ischemia.[3,9,10]

Five of our patients with normal or equivocally abnormal technetium scans subsequently had abnormal gallium scans. The reason for this is unclear but may be explained by the different mechanisms of technetium Tc 99m medronate and gallium citrate Ga 67 concentration in inflamed tissues. The increased gallium citrate Ga 67 uptake is due to the accumulation of in vivo labeled leukocytes, especially polymorphonuclear leukocytes, as well as to the exudation of various in vivo labeled serum proteins. This uptake is not dependent on blood flow and would not be expected to be decreased around areas of ischemia if these were associated with acute inflammation. Although subsequent technetium scans were not obtained, it is possible that these may have been abnormal because of increased osteoblastic activity associated with bone repair. Since the technetium and gallium scans were not performed on the same day, no comparison can be made in this study as to their relative sensitivity in the early detection of acute osteomyelitis. This information is not, to our knowledge, available from the literature.

Lisbona and Rosenthall[11] have suggested that in some cases sequential technetium 99m Tc medronate and gallium citrate Ga 67 scans may help in the diagnosis of acute osteomyelitis. Subtle lesions close to the growth plates were sometimes better seen with gallium scans.

This study was retrospective, and since not every case reviewed has had a technetium scan performed as part of the diagnostic workup, the frequency of falsely normal results for this procedure could not be accurately determined. Forty-nine patients were identified by discharge diagnosis as having acute osteomyelitis; 31 of these had had technetium Tc 99m medronate scans performed, of whom seven were selected for the reported cases.

The purpose of this study is to introduce a note of caution into the report of a normal technetium bone scan in the patient with suspected acute osteomyelitis. A normal bone scan does not rule out this diagnosis. If clinical suspicion is strong, then other steps to confirm the diagnosis, eg, a gallium scan or needle aspiration of the bone, should be performed and appropriate antibiotic therapy begun.

References

1. Gilday DL, Paul DJ, Paterson J: Diagnosis of osteomyelitis in children by combined blood pool and bone imaging. *Radiology* 117:331-335, 1975.
2. Duszynski DO, Kuhn JP, Afshani E, et al: Early radionuclide diagnosis of acute osteomyelitis. *Radiology* 117:337-340, 1975.
3. Handmaker H, Leonards R: The bone scan in inflammatory osseous disease. *Semin Nucl Med* 6:95-105, 1976.
4. Letts RM, Afifi A, Sutherland JB: Technetium bone scanning as an aid in the diagnosis of atypical actue osteomyelitis in children. *Surg Gynecol Obstet* 140:899-902, 1975.
5. Treves S, Khettry J, Broker FH, et al: Osteomyelitis: Early scintigraphic detection in children. *Pediatrics* 57:173-186, 1976.
6. Garnett ES, Cockshott WP, Jacobs J: Classical acute osteomyelitis with a negative bone scan. *Br J Radiol* 50:757-760, 1977.
7. Lentle BC, Russel AS, Percy JS, et al: Bone scintiscanning updated. *Ann Intern Med* 84:297-302, 1976.
8. Waldvogel FA, Medoff G, Swartz MN: Osteomyelitis: A review of clinical features, therapeutic considerations, and unusual aspects: Part 1. *N Engl J Med* 282:198-206, 1970.
9. Russin LD, Staab EV: Unusual bone-scan findings in acute osteomyelitis: Case report. *J Nucl Med* 17:617-619, 1976.
10. Trackler RT, Miller KE, Sutherland DH, et al: Childhood pelvic osteomyelitis presenting as a "cold" lesion on bone scan: Case report. *J Nucl Med* 17:620-622, 1976.
11. Lisbona R, Rosenthall L: Observations on the sequential use of ^{99m}Tc phosphate complex and ^{67}Ga imaging in osteomyelitis, cellulitis and septic arthritis. *Radiology* 123:123-129, 1977.

Staphylococcus aureus Sepsis in Childhood Malignancy

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• **Forty-five episodes of *Staphylococcus aureus* septicemia occurred in 44 children with malignant neoplasms over a seven-year period. The most frequent findings at diagnosis were fever, neutropenia, and an active malignant process. Twenty-six (58%) of 45 episodes had a primary focus of infection. Multiple-organism sepsis occurred four times; three episodes were fatal. Only one patient with single-organism *S aureus* sepsis died (a mortality of 2%). Direct infectious complications occurred in nine (20%) of 45 episodes. Endocarditis and osteomyelitis were not seen as complications of *S aureus* sepsis.**

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Staphylococcus aureus is a common cause of infections and bacteremia in children and adults[1,2] though not the most common pathogen in infections acquired by hospitalized patients.[1-6] Although children with cancer have a high incidence of *S aureus* infections,[7] the mortality is low.[8] This differs from the high mortality of *S aureus* sepsis associated with acute endocarditis seen in heroin addicts[9,10] and in patients without a primary site of infection.[2] Recent studies suggest that patients who have a primary site of infection[2] or a removable focus of infection[11] almost never have bacterial endocarditis. As in a previous study,[8] bacterial endocarditis was not seen in our patient. Our study confirms and extends the observation that the mortality due to *S aureus* sepsis in children with cancer is low[8] but reports a notable (20%) infectious-complication rate.

METHODS

The medical records of all oncology patients at the Children's Orthopedic Hospital and Medical Center, Seattle, from January 1972 to July 1977, and the medical records of all oncology patients at Columbus (Ohio) Children's Hospital from January 1978 to July 1979 who had a documented episode of *S aureus* sepsis were reviewed.

Established criteria were used to assess the clinical significance of staphylococcal isolates from blood.[12] All cases were examined for localized foci of staphylococcal infection. If a lesion was found at initial presentation, it was classified as a primary focus of staphylococcal infection that led to bacteremia. If the lesion developed after the first hospital day, it was arbitrarily defined as a secondary focus.

Blood cultures were obtained by inoculating venous blood directly into bottles containing Trypticase soy broth under partial vacuum. *Staphylococcus aureus* was identified using routine bacteriologic methods. Susceptibility of isolates to antibiotics was determined by a single-disk diffusion method.[13]

The complete blood cell count was obtained using an automatic cell counter,[14] and the absolute neutrophil count was determined by multiplying the percentage of polymorphonuclear leukocytes in the differential cell count by the leukocyte count.

The following information was found: primary site of infection, sensitivity of the organism to penicillin, response to therapy, and secondary staphylococcal infectious complications during or following therapy.

RESULTS

Patient Population

Forty-five episodes of staphylococcal sepsis occurred in 44 patients (27 boys, 17 girls). Thirty-six episodes occurred in patients with hematologic malignant neoplasms (leukemia or lymphoma), whereas nine occurred in patients with a malignant solid tumor (Table 1). Unlike a previous study,[8] this distribution did not reflect the distribution of these diagnoses in the total patient population.

Thirty-four (76%) of the children were in relapse of the malignancy and 31 (69%) were neutropenic (absolute neutrophil count, < 500/cu cm). Four of the 11 episodes in remission occurred in patients who had previous-

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Table 1.—Mortality due to *Staphylococcus aureus* Sepsis in Relation to Absolute Neutrophil Count, Underlying Disease, and Disease Status

	Absolute Neutrophil Count/cu cm			
	No. of Episodes/No. Fatal Episodes			
	< 500	500-1,000	> 1,000	Total
S aureus alone				
Hematologic malignant neoplasms				
Remission	2/0	1/0	6/0	**9/0**
Relapse	23/1	1/0	2/0	**26/1**
Solid tumor				
Remission	1/0	0/0	0/0	**1/0**
Relapse	1/0	0/0	4/0	**5/0**
S aureus plus another organism				
Hematologic malignant neoplasms				
Remission	0/0	0/0	0/0	**0/0**
Relapse	1/1	0/0	0/0	**1/1**
Solid tumor				
Remission	1/1	0/0	0/0	**1/1**
Relapse	2/1	0/0	0/0	**2/1**
Total	**31/4**	**2/0**	**12/0**	**45/4**

Table 2.—Secondary Complications of *Staphylococcus aureus* Sepsis in Relation to Absolute Neutrophil Count, Underlying Disease, and Disease Status

	Absolute Neutrophil Count/cu cm			
	No. of Episodes/No. of Complications			
	< 500	500-1,000	> 1,000	Total
Hematologic malignant neoplasms				
Remission	2/0	1/0	6/3	**9/3**
Relapse	24/5	1/0	2/1	**27/6**
Solid tumors				
Remission	2/0	0/0	0/0	**2/0**
Relapse	3/0	0/0	4/0	**7/0**
Total	**31/5**	**2/0**	**12/4**	**45/9**

ly undergone allogeneic bone marrow transplantation.

The Organism and the Infection

Forty-four of the 45 isolates were tested for antibiotic sensitivity; 36 (82%) were resistant to penicillin. Single-organism sepsis occurred in 41 (91%) of 45 episodes. *Staphylococcus aureus* sepsis was complicated by *Candida* organisms in two episodes and by *Escherichia coli* in the remaining two episodes.

A primary site of infection was identified in 26 (58%) of 45 episodes. The most common primary sites were an infected finger secondary to finger puncture for blood sampling (six episodes), followed in frequency by miscellaneous skin lesions (four episodes), lip lesions (four episodes), infected hyperalimentation lines (three episodes), mouth sores (two episodes), chicken pox lesions (two episodes), and an intravenous catheter, a pierced ear lobe, a biopsy site, a paracentesis site, and a soft tissue abscess (one episode each). Colonization occurred in five other individuals in one or more sites not clinically infected.

Treatment

All patients were initially treated with an aminoglycoside and a cephalosporin or with an aminoglycoside and a semisynthetic penicillinase-resistant penicillin. Frequently, therapy was changed to either a cephalosporin alone or a semisynthetic penicillinase-resistant penicillin alone when the sensitivities were known. The duration of therapy varied from ten days to six weeks, as the patients with infectious complications were treated for longer periods.

Mortality

Four episodes ended fatally. Three were associated with multiple-organism sepsis (Table 1), which occurred four times. Only one episode of single-organism sepsis was fatal. All deaths occurred when the absolute neutrophil count was less than 500/cu cm, and three of the four deaths occurred during relapse of the underlying malignant neoplasm. Fatal episodes occurred twice in children with hematologic malignant neoplasms and twice in children with malignant solid tumors.

Complications During Therapy

Secondary staphylococcal infectious complications of *S aureus* sepsis were seen in nine (20%) of 45 episodes and included liver and abdominal wall abscesses in two episodes, pneumonia in two episodes, meningitis in two episodes, and a chest wall and pleural abscess, multiple soft tissue abscesses, and the scalded skin syndrome seen in one episode each. Secondary complications occurred in both neutropenic and nonneutropenic patients and in both remission and relapse. All of the complications occurred in children with leukemia (Table 2).

In two (22%) of the nine episodes with staphylococcal infectious complications, there was a clearly definable primary focus, compared to the overall population in which 58% had a primary focus. Notably, there were no episodes of acute staphylococcal osteomyelitis or endocarditis.

COMMENT

The incidence of *S aureus* in children with cancer has been estimated to be from 10% to 27%.[7,15] Despite this high incidence, we found a mortality from *S aureus* sepsis alone to be 2%, compared with the mortality described in adults and children without malignant neoplasms, which has ranged from 11% to 78%.[1,2,5,6,16,17] In a previous study of *S aureus* infections in children with cancer, the overall mortality was 30%.[8] However, only 4% could be directly related to *S aureus* infection and 13% were in some part related to *S aureus* infection.[8] Our study confirms that the mortality from *S aureus* sepsis uncomplicated

by a second bacterial or fungal organism is low (one of four cases), as is the overall mortality (four of 45 cases). Multiple-organism sepsis, as in previous studies,[18] was highly fatal, three of four episodes resulting in death. Of the four deaths in our series, all occurred in patients whose absolute neutrophil count was less than 500/cu cm, three of the four occurred in relapse, and three were associated with other infections.

The major complications of *S aureus* infections include endocarditis,[9,10] osteomyelitis,[19] meningitis,[20,21] pneumonia,[22-24] disseminated abscesses,[25] and the scalded skin syndrome.[26] In a review of a series of *S aureus* sepsis, Cluff et al found that 35% of individuals had metastatic staphylococcal abscesses demonstrated by roentgenogram, surgical drainage, or at postmortem examination.[5] Nolan and Beaty[2] reviewed 105 cases of *S aureus* bacteremia and found two clinical patterns, separable according to the presence of an identifiable primary staphylococcal infection. Of the patients in their series who had a primary site, the incidence of endocarditis or of a secondary staphylococcal focus was very low, whereas bacteremia not associated with a primary site was associated with a high incidence of endocarditis and secondary foci of staphylococcal infections. Furthermore, Iannini and Crossley[11] reviewed 29 cases of *S aureus* bacteremia associated with a removable focus of infection and found no cases of endocarditis or secondary foci of infection. As in a previous review,[8] a primary site of infection was common in our patients, occurring in 26 (58%) of 45 episodes. However, of these 26 patients, only two (8%) had a secondary staphylococcal complication, whereas of the 19 patients without a primary site, seven (37%) had a secondary infectious complication. These observations support the findings of the two previous adult series[2,11] that an *S aureus* bacteremia associated with a removable focus of infection or with a primary site is usually not complicated by a secondary site of infection.

Although endocarditis was not found by clinical or laboratory evaluation or by autopsy examination, secondary complications of staphylococcal infections in our series occurred in nine (20%) of 45 episodes. This was much higher than the three secondary staphylococcal complications seen in a series of 70 episodes of *S aureus* bacteremia in children with cancer reported by Ladisch and Pizzo.[8] Further evaluation of the secondary staphylococcal complications in our series revealed no differences in therapy and no relationship to absolute neutrophil count or remission status. All complications occurred in children with leukemia.

The low mortality may have been related to early institution of antibiotic therapy. However, the morbidity was appreciable, and prompt treatment with antibiotics did not prevent secondary staphylococcal complications. Children with *S aureus* bacteremia who have been treated with immunosuppressive therapy must be watched closely for complications and secondary foci of staphylococcal infection, especially when there is no primary site of infection.

References

1. Hieber JP, Nelson AJ, McCracken GH: Acute disseminated staphylococcal disease in childhood. *Am J Dis Child* 131:181-185, 1977.
2. Nolan CM, Beaty HN: *Staphylococcus aureus* bacteremia: Current clinical patterns. *Am J Med* 60:495-500, 1976.
3. Wise RI: Modern management of severe staphylococcal disease. *Medicine* 52:295-304, 1973.
4. Allen JD, Roberts CE, Kirby WMM: Staphylococcal septicemia treated with methicillin. *N Engl J Med* 266:111-116, 1962.
5. Cluff LE, Reynolds RC, Page DL, et al: Staphylococcal bacteremia and altered host resistance. *Ann Intern Med* 69:859-873, 1968.
6. Faber V, Jessen O, Rosendal K, et al: Staphylococcal bacteremia: Clinical and bacteriologic observations in 201 cases. *Br Med J* 2:1832-1837, 1960.
7. Chilcote RR, Bachner RL: Septicemia in association with acute lymphoblastic leukemia. *J Pediatr* 94:715-718, 1979.
8. Ladisch S, Pizzo PA: *Staphylococcus aureus* sepsis in children with cancer. *Pediatrics* 61:231-234, 1978.
9. Louria DB, Hensle T, Rose J: The major complications of heroin addiction. *Ann Intern Med* 67:1-22, 1967.
10. Cherubin CE, Baden M, Kaveler F, et al: Infective endocarditis in narcotic addicts. *Ann Intern Med* 69:1091-1098, 1968.
11. Iannini PB, Crossley K: Therapy of *Staphylococcus aureus* bacteremia associated with a removable focus of infection. *Ann Intern Med* 84:558-560, 1976.
12. MacGregor RR, Beaty HN: Evaluation of positive blood cultures: Guidelines for early differentiation of contaminated from valid positive cultures. *Arch Intern Med* 130:84-87, 1972.
13. Bauer AW, Kirby WMM, Sherris JC, et al: Antibiotic susceptibility testing by a standardized single-disk method. *Am J Clin Pathol* 45:493-495, 1966.
14. Richar WJ, Breakwell ES: Evaluation of an electronic particle counter for the counting of white blood cells. *Am J Clin Pathol* 31:384-386, 1959.
15. Bodey GP: Infections in cancer patients. *Cancer Treat Rev* 2:89-128, 1975.
16. Shulman ST, Ayoub EM: Severe staphylococcal sepsis in adolescents. *Pediatrics* 58:59-66, 1976.
17. Wilson R, Hamburger M: Fifteen years' experience with *Staphylococcus* septicemia in acute leukemia. *Am J Med* 22:437-457, 1957.
18. Bodey GP, Nies BA, Freireich EJ: Multiple organism septicemia in acute leukemia. *Arch Intern Med* 116:266-272, 1965.
19. Waldrogel FA, Medoff G, Schwartz MN: Osteomyelitis: A review of clinical features, therapeutic considerations and unusual aspects. *N Engl J Med* 282:198-206, 260-268, 316-322, 1970.
20. Studdert TC: Staphylococcal spinal meningitis. *Br Med J* 1:1457-1459, 1958.
21. Swartz MN, Dodge PR: Bacterial meningitis: A review of selected aspects. *N Engl J Med* 272:779-787, 1965.
22. Highman JH: Staphylococcal pneumonia and empyema in childhood. *Amer J Roentgen* 106:103-108, 1969.
23. Miller WR, Jay AR: Staphylococcal pneumonia in influenza: Five cases. *Arch Intern Med* 109:276-286, 1962.
24. Wise MB, Beaudry PH, Bates DV: Long-term follow-up of staphylococcal pneumonia. *Pediatrics* 38:398-401, 1966.
25. Anand SV, Evans KT: Pyomyositis. *Br J Surg* 51:917-920, 1964.
26. Melish ME, Glasgow LA: Staphylococcal-scaled skin syndrome: The expanded clinical syndrome. *J Pediatr* 78:958-967, 1971.

Immunoglobulin Concentrations in Duodenal Fluid of Infants and Children

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• **The immunoglobulin content of duodenal fluid in children at different ages has not as yet been determined, while that of serum, feces, and saliva has been well established. In 92 normal infants, children, and young adults on whom duodenal intubation was performed, duodenal fluid IgA, IgM, and IgG levels were measured. From these data, a developmental profile of immunoglobulins in duodenal fluid from 2 weeks of life to 19 years was obtained. Duodenal fluid IgA, IgM, and IgG appeared to maintain rather constant levels. The grand mean IgA level was lower than the grand mean IgG level (12.7 ± 0.8 vs 29.1 ± 2.5 mg/g of protein). Secretory component was detected in all duodenal fluids. IgG concentrations were greater than those of IgM (29.1 ± 2.5 vs 13.2 ± 1.4 mg/g of protein) over all age ranges. The developmental patterns of all immunoglobulins appeared to be different from those observed in serum or saliva with the exception of duodenal fluid IgA, which has a pattern similar to that of salivary IgA.**

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Immunoglobulins found in duodenal fluid have been reported to originate from gastric,[1] pancreatic,[2] bile,[3] and small intestine secretions.[4] The pathways for transepithelial transfer of these immunoglobulins have not been completely defined.[5] To our knowledge, the age-related changes of duodenal fluid immunoglobulins have not been reported, while those of serum,[6] feces,[7] and saliva[8,9] have been observed.

Serum IgA has generally not been detected in newborns, and serum IgM has been found only in small amounts.[6] IgG has been found to be the predominant serum immunoglobulin in infancy.[6] IgA levels in human fecal material were very low in the newborn.[7] In the saliva, IgA has not been detected until 1 week of age, while IgG has been found to be present only temporarily.[8] Human salivary IgM has not been detected at any age.[8]

Estimates of immunoglobulin concentrations in the upper small intestine varies considerably among researchers.[4,10,11] It is the aim of this report to provide an overview of the development of immunogobulins in the normal human duodenum from 2 weeks to 19 years of age. In addition, the reliability and validity of the determination and the technique of fluid collection were investigated.

SUBJECTS AND METHODS

Subjects

A group of 92 infants and children, between the ages of 2 weeks and 19 years, were selected as normal subjects from approximately 250 patients undergoing pancreozymin-secretin testing. Informed consent was obtained from all parents of infants and children undergoing the pancreozymin-secretin test as well as measurement of pancreatic enzymes and immunoglobulins. The subjects included 24 infants, 1 month of age and older, who were siblings of patients with cystic fibrosis, investigated under a special protocol, and found to be disease-free. The largest number of subjects (68) came from a group of patients evaluated for failure to thrive or history of chronic diarrhea and found to have no gastrointestinal disease. They had no evidence of pancreatic disorders or small intestinal mucosal injury. All subjects in this study had normal serum albumin and globulin levels. There was no appreciable difference between these two groups with respect to the variables measured in the study. The assignment of age groups was arbitrary according to Haneberg and Aarskog.[7]

Handling of Duodenal Fluids

After an overnight fast, duodenal intubation was performed under fluoroscopic control, using a double-lumen Dreiling tube. The tip of the tube was positioned in the area of the ligament of Trietz.[12] In newborn infants receiving nasojejunal feeding, a gastric tube was added after four hours of fasting. Duodenal fluid was collected for 20 minutes in flasks cooled on ice. At times, gentle aspiration was used to collect the specimens. The specimens were immediately frozen and stored at −20 °C.

Quantitation of Immunoglobulins

IgG, IgA, and IgM were quantitated by single radial immunodiffusion techniques of Mancini,[13] by use of commercially available equine or goat antisera that were monospecific for the heavy chains of human IgG, IgM, and IgA (7S).

All determinations of IgA in duodenal fluid were carried out using goat antibodies against 7S IgA. Colostrum was used as a standard in an attempt to determine the percentage of antibodies that are 7S and 11S.

The Fahey-McKelvey technique[14] was used to construct standardization curves correlating the concentration of immunoglobulins in the duodenal fluid sample with its corresponding precipitation ring diameter. Semilogarithmic paper was used to produce a linear relationship between the two variables. The plates were incubated at 23 °C and read at 18 ± 0.5 hours after the wells had been filled.

Quality Control Analysis

Lyophilized human serum and colostrum were used as a quality control measure. The data were well within the standardization range of each immunoglobulin. A number of samples were thawed after storage at −20 °C for five to six months to determine immunoglobulin loss during storage. There was no significant difference. Several of the subjects' test results were examined for evidence of any variation within each group of the examination and found to be consistent.

The presence of secretory component in the duodenal fluid was tested by use of double radial immunodiffusion plates (Ouchterlony 1% agar gel). Rabbit antiserum to human IgA (α chain) was placed in the center wall of one plate (Fig 1, top), and rabbit antiserum to human secretory component was placed in the center well of another plate (Fig 1, bottom). The specimens (duodenal fluid, human pooled serum, colostrum, saliva, and amniotic fluid) were placed in each of six outside wells; their cross reactivity with the antiserum was checked after incubation for 12 to 24 hours at room temperature.

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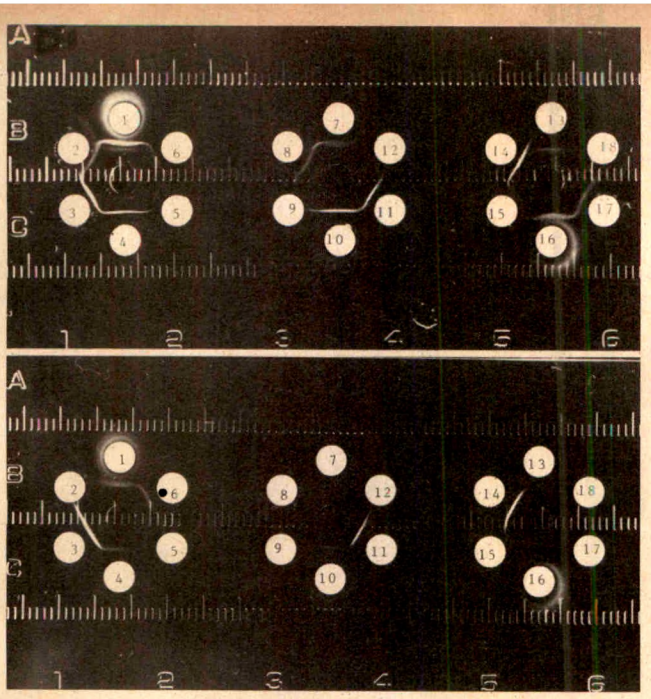

Fig 1.—Top, Double radial immunodiffusion with rabbit antiserum to human anti-IgA (α chain) in center wells. Bottom, Double radial immunodiffusion with rabbit antiserum to human secretory component in center wells. Outer wells were numbered and contained following substances: wells 1, 4, 7, 10, 13, and 16, duodenal fluids from children aged 4 to 16 months; wells 3, 11, and 14, human colostrum; wells 5, 12, and 18, human amniotic fluid obtained at 28 to 42 weeks' gestation; wells 6, 9, and 15, human saliva from children aged 2 to 12 years; wells 2, 8, and 17, human serum from children aged 2 to 17 years.

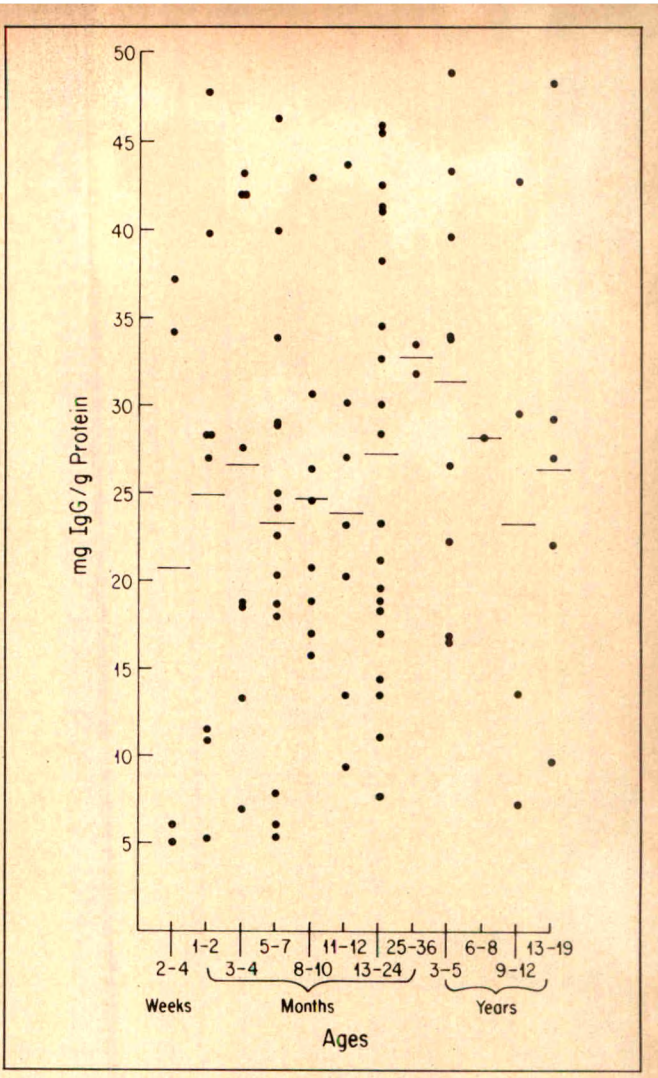

Fig 2.—Human duodenal fluid IgG levels from 2 weeks to 19 years of age.

The possible continued alteration of immunoglobulins in the duodenal fluid during the incubation period due to the presence of endopeptidases and exopeptidases secreted by the pancreas was tested.

A sample control of fixed-ratio serum and duodenal fluid immunoglobulin were incubated. No significant changes were observed in the immunoglobulin levels.

Statistical Analysis

Analysis of the data was performed to determine differences in concentrations of IgA, IgM, and IgG that might exist between age groups. Analysis was accomplished by a one-way multivariate analysis of variance[15] for three dependent variables (IgA, IgM, IgG) across 13 age groups (1 × 13 MANOVA). The analysis was executed by means of a prepared statistical computer program that simultaneously performs univariate analyses of variance for each dependent variable (1 × 13 ANOVA).

RESULTS

Double radial immunodiffusion with rabbit antiserum to human anti-IgA (α chain) (Fig 1, top) demonstrated precipitation lines in all the duodenal fluids, human colostrum, and human serum tested. Human saliva and amniotic fluid showed faint precipitation lines. Double radial immunodiffusion with rabbit antiserum to human secretory component (Fig 1, bottom) demonstrated heavy precipitation lines with colostrum. Less pronounced lines were seen with human duodenal fluid and saliva. No precipitation lines were observed with human amniotic fluid or serum.

The values obtained for each immunoglobulin at each age are seen in Fig 2, 3, and 4. The data are presented per grams of protein and per deciliters of fluid. The results of the 1 × 13 MANOVA indicated that no statistically significant differences existed between any of the age groups (F [36,115.96] = 1.117; $P < .47$), although significant differences existed between the values of the various immunoglobulins (F [3,39] = 112.07; $P < .0001$). The concentration of protein in duodenal fluid ranged from 0.34 to 0.81 g/dL, with a mean of 0.52 g/dL.

IgG Levels in Duodenal Fluid

The concentration of IgG per gram of protein maintained a rather constant level throughout the age ranges studied (ANOVA: F [12,41] = 1.03; $P < .43$). No statistical significance was noted between the ages. IgG concentrations were also observed to be higher than those of either IgA or IgM over all age ranges (ANOVA: F [1,41] = 23.867; $P < .0001$) (Fig 2, 3, and 4).

The concentration of IgG per deciliter of fluid showed a similar level throughout the age ranges studied. IgG levels per deciliter of fluid were also observed to be higher than either IgA or IgM levels.

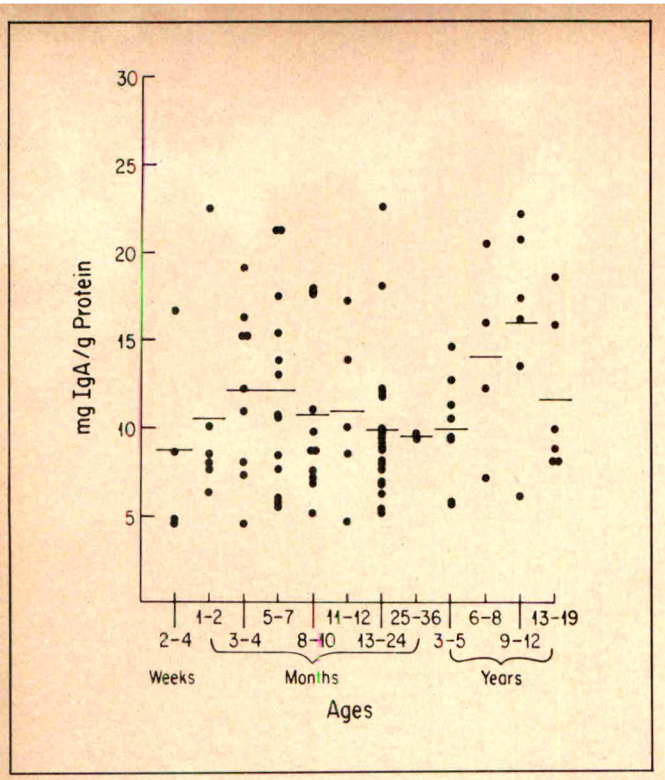

Fig 3.—Human duodenal fluid IgA levels from 2 weeks to 19 years of age.

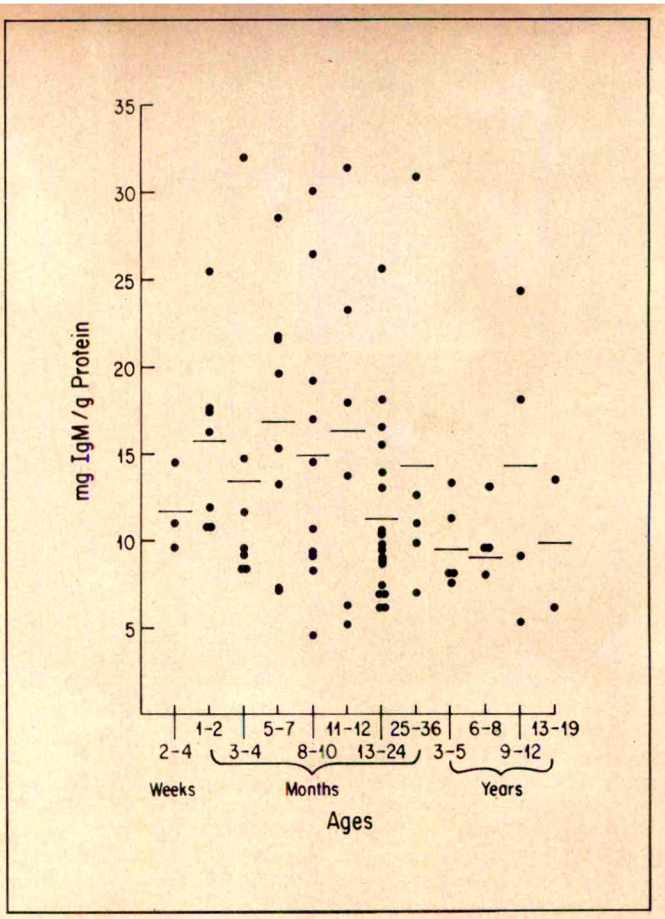

Fig 4.—Human duodenal fluid IgM levels from 2 weeks to 19 years of age.

IgA Levels in Duodenal Fluid

The IgA levels per gram of protein in duodenal fluid were similar in all age groups studied (ANOVA: F [12,41] = .68; $P < .75$).

IgA levels per deciliter of fluid also maintained similar levels throughout the studied ages.

IgM Levels in Duodenal Fluid

As with IgA levels, the levels of IgM per gram of protein in duodenal fluid persisted through all the ages tested (ANOVA: F [12,41] = 183; $P < .62$).

Similar results were obtained with IgM per deciliter of fluid, where a similar level was observed over all ages studied.

COMMENT

There is concern with the techniques used in duodenal fluid immunoglobulin analysis. Shearman and colleagues[16] have reviewed the problems of accurate quantitation of immunoglobulin concentrations in the intestinal fluid. Immunoglobulins are susceptible to proteolytic digestion: IgA to pepsin and IgG and IgM to trypsin.[17] A number of techniques have been used in attempting to overcome this problem. They include heating, cooling, and the addition of antitryptic agents.[18] None of these precautions has met with complete success, as evidenced by the presence of immunoglobulin fragments in duodenal secretions.[17] This indicates that some proteolysis may have taken place and may lead to overestimation of immunoglobulin concentrations, with only semiquantitative results being obtained. The developmental patterns of duodenal fluid immunoglobulin levels remain unchanged as all levels are assumed to be affected equally.[12] The specimens used in this study were frozen immediately after collection to minimize deterioration of immunoglobulin content that would adversely effect the results. There is a possibility of continued alteration of Ig molecules by duodenal enzymes during the radioimmunodiffusion procedure. To test this possibility, we inoculated a fixed ratio of serum with duodenal fluid of known Ig quantity and found no changes in the expected values.

We observed double precipitation rings in 7% of the single radial immunodiffusion testing plates. These rings were reported by Plaut and Keonil[18] and Kraft et al.[19] The rings are presumed to be nonspecific precipitation lines between antisera and a mucopolysaccharide in the duodenal fluid.[19] These plates were not included in compiling the final data.

Serum IgA in man is predominantly a 7S monomer, while secretory IgA, as found in duodenal fluid and saliva, is predominantly an 11S dimer. As stated earlier, all the samples used in this analysis contained secretory component. In the quantitation of IgA in duodenal fluid, the IgA reference serum is of the 7S variety, while the IgA in the specimen is both 7S and 11S. This, therefore, must lead to an underestimate of the duodenal fluid level of IgA. Hobbs,[20] studying pure 11S IgA as found in human saliva, reported a correction factor of 1.4 to determine the correct IgA level. However, duodenal fluid IgA contains both 11S and some 7S IgA.[5] We used known amounts of 11S IgA in colostrum as a standard and corrected the 7S IgA standard of the available antisera.

The sources of IgA and IgM that

enter the duodenum are believed to be the plasma cells located in the lamina propria of the intestinal mucosa.[21-23] These immunoglobulins have been assumed to interact with secretory component, a receptor on the surface of or within intestinal cells in the crypt region, after diffusion across the basement membrane.[24] Subsequently, it was suggested that IgA and IgM are transported through the epithelial cell and secreted into the duodenum by exocytosis.[25] The source of IgG in the duodenum has been assumed to be the serum, as the mucosa contains relatively few IgG-containing cells.[23] IgG enters the lumen of the duodenum by the same nonspecific mechanism common to other plasma proteins.[25]

In this study, there was no statistical difference in duodenal fluid immunoglobulin concentrations from 2 weeks through 19 years of age. The IgA developmental patterns were found to be different from those seen with IgA in serum.[6] IgG levels were approximately twice those of IgA or IgM.

The development of immunoglobulins in human serum from infancy through adulthood has been well established.[6,26-29] IgA has been detected in the cord sera of some infants. Serum IgA levels increase over the first months of life to reach almost one quarter of the adult levels by the age of 1 year, and 50% of the adult levels by 3½ years of age.[26] Serum IgG levels drop during the first four months of life to approximately one half of the adult level and thereafter increase rapidly up to 1 year of age, finally reaching adult levels by the age of 7 years.[6] Serum IgM concentrations are very low at birth, but increase steadily so that 50% of adult concentration is reached at 4 months of age, and adult levels are attained at approximately 1 to 2 years of age.[6]

Haneberg and Aarskog[7] measured IgA in human fecal material and demonstrated minimal levels of antibody at 1 to 3 days of life. This was followed by a rapid increase in IgA level to a peak at 1 to 2 months of age and a constant level was then observed at a value approximately one-fifth the peak value.[7] This plateau occurred at 1 year of age and continued as such into adult life.[7]

Selner et al[8] measured the concentration of immunoglobulins in human saliva. IgA was not detected at birth, but appeared by 1 week of life. By 4 weeks of age, 92% of the infants had adult levels of IgA in their saliva. IgM was not detected. IgG was temporarily present in the saliva prior to 10 days of age, but disappeared as IgA concentrations increased.[8] It was postulated that this temporary IgG level in the saliva may represent "leakage" from the serum due to the increased permeability of the mucous membranes to protein during the early postnatal period.[8,30,31] Brandtzaeg et al[9] reported IgA concentrations in human saliva predominating over those of IgG.

In our studies, the pattern of development for IgG, IgA, and IgM in duodenal fluid was quite different from that reported for human serum.[6,27,29] IgA and IgM levels in duodenal fluid remained relatively constant through the age ranges studied. In our study and in other observations,[21-23] IgM is present in duodenal fluid. This is in contrast to saliva, in which IgM was not detected at any age.[30] In addition, the developmental patterns observed with salivary IgA represent sequences similar to those seen with duodenal fluid IgA.[8]

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W. Allan Walker, MD, reviewed the manuscript. Pearay L. Ogra, MD, and Byung Hak Park, MD, helped design and execute the project and also reviewed the manuscript. Gary Graber, PhD, did the statistical analysis. Mary Lou Stein provided secretarial assistance.

References

1. McClelland DBL, Finlayson NDC, Samson RR, et al: Quantitation of immunoglobulins in gastric juice by electroimmunodiffusion. *Gastroenterology* 60:509-514, 1971.

2. Soto J, Bramis J, Acfses AH, et al: The pancreas and immunoglobulins: I. Immunoglobulin levels in pancreatic secretion of patients with normal function: Preliminary studies. *Am J Gastroenterol* 67:345-347, 1977.

3. Lemaitre-Coelho I, Jackson GDF, Yaerman J: High levels of secretory IgA and free secretory component in the serum of rats with bile duct obstruction. *J Exp Med* 147:934-939, 1977.

4. Savilahti E: Immunoglobulin containing cells in the intestinal mucosa and immunoglobulins in the intestinal juice of children. *Clin Exp Immunol* 11:415-425, 1972.

5. Clancy R, Bienenstock J: Secretion of immunoglobulins. *Clin Gastroenterol* 5:229-249, 1976.

6. Allansmith M, McCleelan BH, Butterworth M, et al: The development of immunoglobulin levels in man. *J Pediatr* 72:276-290, 1968.

7. Haneberg B, Aarskog D: Human fecal immunoglobulins in healthy infants and children, and in some with diseases affecting the intestinal tract or the immune system. *Clin Exp Immunol* 22:210-222, 1975.

8. Selner JC, Merrill DA, Claman HN: Salivary immunoglobulins and albumin: Development during the newborn period. *J Pediatr* 72:685-693, 1968.

9. Brandtzaeg P, Fjellangen I, Gjeruldsen ST: Human secretory immunoglobulins: I. Salivary secretions from individuals with normal or low levels of serum immunoglobulins. *Scand J Hematol* 83(suppl 12):1, 1970.

10. Richman LK, Brown WR: Immunochemical characterization of IgM in human intestinal fluid. *J Immunol* 119:1515-1519, 1977.

11. Plaut AG, Prayoonsri K: Immunoglobulins in human small intestinal fluid. *Gastroenterology* 56:522-530, 1969.

12. Lebenthal E, Shwachman H: The pancreas: Development, adaptation and malfunction in infancy and childhood. *Clin Gastroenterol* 6:397-413, 1977.

13. Mancini G, Carbonara AO, Heremans JF: Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 2:235-254, 1965.

14. Fahey JL, McKelvey EM: Quantitative determination of serum immunoglobulins in antibody-agar plates. *J Immunol* 94:84-90, 1965.

15. Morrison DF: *Multivariate Statistical Methods*. New York, McGraw-Hill Book Co Inc, 1976.

16. Shearman DJC, Pankin DM, McClelland DBL: The demonstration and function of antibodies in the gastrointestinal tract. *Gut* 13:483-499, 1972.

17. Samson RR, McClelland DBL, Shearman JC: Studies on the quantitation of immunoglobulin in human intestinal secretions. *Gut* 14:616-626, 1973.

18. Plaut AG, Keonil B: Immunoglobulins in human small intestinal fluid. *Gastroenterology* 56:522-530, 1969.

19. Kraft SC, Rothberg RM, Kriebel GW: Non-immunologic precipitation lines between serum and enteric contents giving false positive evidence for local antibody production. *J Immunol* 104:528-529, 1970.

20. Hobbs JR: Immunoglobulins in clinical chemistry. *Adv Clin Chem* 14:219-225, 1971.

21. Poger ME, Lamm ME: Localization of free and bound secretory component in human intestinal epithelial cells: A model for the assembly of secretory IgA. *J Exp Med* 139:629-642, 1974.

22. Brown WR, Isobe Y, Nakane RK: Studies on translocation of immunoglobulins across intestinal epithelium: II. Immunoelectronmicroscopic localization of immunoglobulins and secretory component in human intestinal mucosa. *Gastroenterology* 71:985-995, 1976.

23. Brown WR: Relationships between immunoglobulins and the intestinal epithelium. *Gastroenterology* 75:129-138, 1978.

24. Brandtzaeg P: Structure, synthesis, and external transfer of mucosal immunoglobulins. *Ann Rev Immunol* 124:417-438, 1971.

25. Walker WA, Isselbacher KJ: Intestinal antibodies. *N Engl J Med* 297:767-773, 1977.

26. Bull DM, Bienenstock J, Tomasi TB: Studies on human intestinal immunoglobulin A. *Gastroenterology* 60:370-380, 1971.

27. Stiehm ER, Fudenberg HH: Serum levels of immune globulins in health and disease: A survey. *Pediatrics* 37:715-727, 1966.

28. West CD, Hong R, Holland NH: Immunoglobulin levels from the newborn period to adulthood and in the immunoglobulin deficiency states. *J Clin Invest* 41:2054-2064, 1962.

29. Fulginiti VA, Sieber OF, Claman HN, et al: Serum immunoglobulin measurement during the first year of life and in immunoglobulin deficiency states. *J Pediatr* 68:723-730, 1966.

30. LoGrippo GA, Hayashi H, Perry M: Immunoglobulins in serum and saliva in health and disease. *Fed Proc* 28:553-558, 1969.

31. South MA, Warwick WJ, Wollheim FA, et al: IgA levels in the serum and saliva of pediatric patients. *J Pediatr* 71:645-653, 1967.

5-Hydroxytryptophan and Pyridoxine

Their Effects in Young Children With Down's Syndrome

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• In a double-blind study, 89 children with Down's syndrome were given 5-hydroxytryptophan or pyridoxine hydrochloride in the first three years of life. The analysis of 5-hydroxyindole blood levels revealed that 5-hydroxytryptophan, pyridoxine, and the combination of 5-hydroxytryptophan and pyridoxine raised blood levels of 5-hydroxyindole equally well in 40% of the children. The assessment of muscle-tone ratings showed no significant difference among the study groups once children with moderate and severe congenital heart disease were excluded. Detailed studies of cognitive-adaptive function of children in the various groups found a significant difference on the Vineland Social Maturity Scale at ages 6, 12, 18, and 36 months; yet the source of significance was a negative interaction affecting children whose parents were able to comply with furnished guidance; these children showed consistently higher levels of accomplishment.

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During the past decades a multitude of treatment modalities for Down's syndrome have been reported.[1-10] In the attempt to improve physical features and mental abilities of the child with Down's syndrome, a variety of medications, including hormones, vitamins, sicca cells, dimethyl sulfoxide, and various combinations of these and other compounds, have been used. The ineffectiveness of the majority of those therapeutic approaches has been discussed in recent publications.[11-13]

5-Hydroxytryptophan was introduced as a form of therapy in Down's syndrome shortly after several investigators had reported decreased 5-hydroxytryptamine (serotonin) levels in peripheral blood in children with this syndrome.[14-19] Bazelon and co-workers noted improvement in muscle tone, reduced tongue protrusion, and increased motor activity in infants with Down's syndrome who had been given 5-hydroxytryptophan.[20] In a subsequent study, the same investigator compared a group of children with Down's syndrome who received 5-hydroxytryptophan with children in a placebo group; no significant difference of development between children in these two groups was found.[21] In 1971, Partington and co-workers reported a controlled trial of 5-hydroxytryptophan administration to children with Down's syndrome. These investigators did not detect any improvement in motor, behavioral, and neurological functions.[22] Weise and co-workers who gave 5-hydroxytryptophan to young children with Down's syndrome also observed that this compound was not effective in accelerating the children's rate of development. Moreover, no discernible behavioral differences between treated and nontreated children were noted.[23]

Encouraged by Bazelon's initial results, the investigations reported here were begun before the previously cited studies were published.[21-23] The primary objective of this study was to evaluate the effects of 5-hydroxytryptophan or pyridoxine hydrochloride administration on motor, social, intellectual, and language development in young children with Down's syndrome.

SUBJECTS AND METHODS

Newborn children with Down's syndrome were recruited from maternity hospitals and obstetric services of general hospitals located in the greater Boston area, other parts of Massachusetts, southern New Hampshire and Vermont, northern Connecticut, and Rhode Island. Before the individual child entered the study, his or her parents were informed of the study's basic goals, its experimental nature, and the double-blind design. The known risks and possible side effects of 5-hydroxytryptophan were explained and those parents who agreed to have their child enrolled in the study signed an approved informed consent form.

In addition to 5-hydroxytryptophan, the administration of pyridoxine (a coenzyme that participates in the decarboxylation of 5-hydroxytryptophan to 5-hydroxytryptamine) had been reported to increase levels of 5-hydroxytryptamine in children with Down's syndrome.[21] To evaluate the individual as well as the combined and interactive effects of 5-hydroxytryptophan and pyridoxine, four study groups were designed: placebo, pyridoxine, 5-hydroxytryptophan, and 5-hydroxytryptophan-pyridoxine. Random assignment to the different study groups was done by our biostatistical consultant from the Harvard School of Public Health, Boston, and transmitted directly to the participating pharmacist so that the evaluation team was unaware of the random assignment.

The various compounds, placebo, pyridoxine, 5-hydroxytryptophan, and 5-hydroxytryptophan-pyridoxine, were provided in capsules indistinguishable from each other and were administered in divided doses of 1 to 2 mg/kg/day of 5-hydroxytryptophan and 5 to 10 mg/kg/day of pyridoxine hydrochloride. The initial dosage was low (1 mg/kg/day of 5-hydroxytryptophan and 5 mg/kg/day of pyridoxine hydrochloride). If no side effects were observed, the dosage was gradually increased to its maximum (2 mg/kg/day of 5-hydroxytryptophan and 10 mg/kg/day of pyridoxine hydrochloride).

A total of 114 newborns with Down's syndrome were admitted to the study during a three-year time period and each child was followed up until his or her third birthday. Of the 114 children, 25 were excluded for various reasons: 13 children died during the course of the study, 12 of whom had had severe congenital heart disease. Ten children withdrew from the study; their parents either had moved out of the area or had had serious social problems that interfered with orderly follow-up. Two other children were excluded from the study; one had mosaic Down's syndrome and the other child's data were incomplete at the time of the study's completion.

Of the 89 children in the final study sample, there were 50 boys and 39 girls. Eighty-six children's karyotypes showed trisomy 21 and three children had D/G translocation Down's syndrome.

After breaking the drug code at the end of the study, it was found that there were 20 children in the placebo group, 23 in the pyridoxine group, 22 in the 5-hydroxytryptophan group, and 24 in the 5-hydroxytryptophan-pyridoxine group. As Table 1 shows, the random assignment of children to the study groups placed more children with moderate and severe congenital heart

Table 1.—Congenital Heart Disease of Children With Down's Syndrome in the Various Study Groups

Study Group	Congenital Heart Disease* A (None)	B (Mild)†	C (Moderate)‡	D (Severe)§	Total
Placebo	12	1	6	1	20
Pyridoxine	17	1	4	1	23
5-Hydroxytryptophan	17	4	1	0	22
5-Hydroxytryptophan-pyridoxine	17	3	1	3	24
Total	**63**	**9**	**12**	**5**	**89**

*In the analysis of the data, groups A and B as well as groups C and D were combined to AB and CD; there was no significant difference between combined groups ($\chi^2 = 6.51$, $df = 3$, $P > .10$).

†Single cardiac defects, such as atrial or ventricular septal defects without pulmonary vascular involvement. These children usually did not require cardiac medications or cardiac surgery. Their growth rate was normal.

‡More complex cardiac problems, such as endocardial cushion defects. These children often required digitalis. Their growth was suboptimal.

§Serious anatomical heart lesions, such as complex endocardial cushion defects, Fallot's tetralogy, etc. These children were often in cardiac failure, and most had pulmonary complications and reduced growth rate.

Table 2.—Selected Antenatal Conditions of Mothers of Children in the Study Groups*

Study Group	Antenatal Infections	Vaginal Bleeding	Significant Medical Conditions†	Mean Duration of Pregnancy, wk
Placebo	5/20	4/20	2/20	39.1
Pyridoxine	4/23	5/23	3/23	39.1
5-Hydroxytryptophan	7/22	10/22	8/22	38.1
5-Hydroxytryptophan-pyridoxine	4/24	3/24	6/24	38.0

*None of the conditions showed significant differences among the study groups at the 5% level.

†Toxemia, endocrine disorders, serious psychiatric disease, documented nutritional inadequacies, major surgical intervention, etc.

Table 3.—Selected Perinatal Conditions in the Study Groups*

Study Group	Complication During Labor†	Difficulties During Delivery‡	Apgar Score 8 at 5 min	Mean Birth Weight, kg
Placebo	4/20	4/20	4/20	3.25
Pyridoxine	9/23	3/23	2/23	3.17
5-Hydroxytryptophan	2/22	4/22	2/22	2.82
5-Hydroxytryptophan-pyridoxine	4/24	5/24	3/24	3.03

*f test between groups significant, $P < .05$ for birth weights; the other conditions are not significantly associated with study groups.

†Premature separation of placenta, placenta previa, increased blood loss, interuterine fetal distress, meconium-stained amniotic fluid, significantly prolonged labor, etc.

‡Abnormal presentations, cephalopelvic disproportion, high forceps delivery, prolonged compression of umbilical cord, significant blood loss, etc.

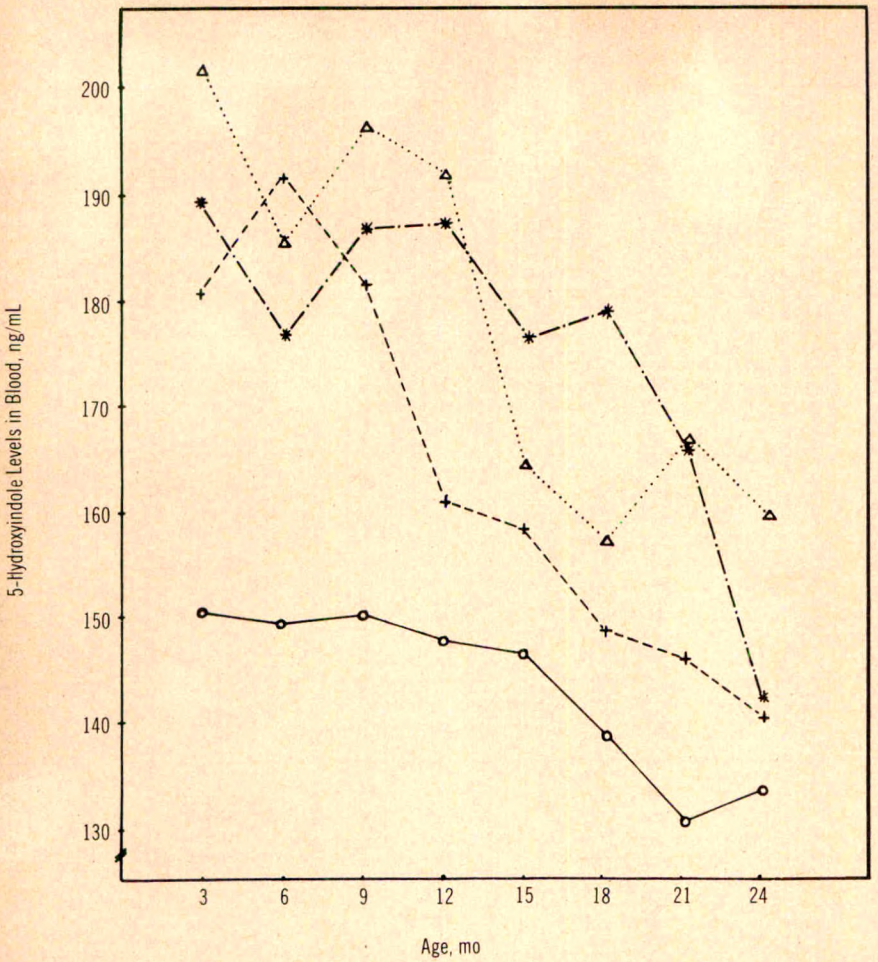

Fig 1.—Mean 5-hydroxyindole levels in blood of children with Down's syndrome according to study group. Circles indicate placebo group; crosses, pyridoxine group; triangles, 5-hydroxytryptophan group; and asterisks, 5-hydroxytryptophan-pyridoxine group. Since after 24 months less than 50% of blood 5-hydroxyindole levels were available, we did not include these incomplete data in this figure.

Table 4.—Means and SE of 5-Hydroxyindole Blood Levels According to Age and Study Group, ng/mL

	Age, mo							
	3	6	9	12	15	18	21	24
Placebo								
Mean	150.3	149.2	151.0	147.8	146.6	138.9	130.2	133.3
SE	11.3	10.8	11.1	11.4	9.9	6.7	7.4	8.3
Pyridoxine								
Mean	180.3	191.5	181.7	165.3	158.4	145.4	146.8	140.7
SE	15.9	13.2	11.4	9.1	8.6	11.3	7.6	7.8
5-Hydroxytryptophan								
Mean	201.3	185.1	196.6	191.8	164.1	157.4	166.8	159.9
SE	19.3	15.0	12.3	13.7	13.0	11.6	11.1	10.4
5-Hydroxytryptophan-pyridoxine								
Mean	189.1	176.7	186.9	187.7	176.6	179.5	165.7	142.6
SE	14.1	16.2	14.0	16.2	14.2	10.3	12.6	9.3

disease in the placebo group (seven children) than in the 5-hydroxytryptophan group (one child). Therefore, in making certain specified analyses, children with moderate and severe cardiac conditions were excluded.

Consideration was given to factors that might have influenced the development of the young children with Down's syndrome during antenatal and perinatal periods. Tables 2 and 3 gives summary statements of selected variables, which indicate that there was acceptable comparability among the randomized study groups, and no significant difference was found except that the mean birthweight of children in the 5-hydroxytryptophan group was significantly lower than the mean birth weight of children in the other study groups. However, during the remainder of the study period there was no statistically significant difference of mean weights of children in the four study groups.

Laboratory investigations performed at three-month intervals focused primarily on total 5-hydroxyindole determination in the blood of all infants with Down's syndrome. This was done according to the procedures described by Rosner and co-workers,[14] which is a modification of Udenfriend et al's previously reported method.[24] The 5-hydroxytryptamine content in the total 5-hydroxyindole determination is 99%, and 1% is 5-hydroxyindole acetic acid.[25] At the end of the study, several parents did not want blood taken from their children, so that only limited laboratory data were available beyond the 24 to 30 month period.

The muscle tone of the children in the study was evaluated independently by three examiners: pediatrician, neurologist, and physical therapist, each of whom followed his or her individual protocols. During the physical examinations, the pediatrician recorded a composite score for muscle tone, ranging from 0 (extremely poor muscle tone) to 4 (hypertonic). The neurologist rated separately muscle tone of upper extremities, lower extremities, neck, and trunk; in addition, posture, arm recoil, leg recoil, ventral suspension, and traction responses were recorded. The individual assessments were averaged to produce a single muscle tone score for each examination. The physical therapist focused on resistance against passive movements in trunk, hip, knees, and elbows. An average score was obtained from each examination.

The cognitive-adaptive function of children in the study was evaluated using the Bayley Scales of Infant Development[26] and the Vineland Social Maturity Scale.[27] Both instruments were given at six-month

intervals during the study period. At the third birthday, each child's language abilities were examined using the Receptive-Expressive Emergent Language Scale (REEL).[28]

Support to parents and instructions regarding various aspects of care and stimulation were provided throughout the study.[29] The parents' ability to comply and follow through with the furnished guidance was rated as *yes* or *no* by the participating nurse after lengthy interviews with the parents at six-month intervals. The individual ratings were summed in the final analysis of the data.

RESULTS

In the analysis of the total 5-hydroxyindole concentration in blood of children with Down's syndrome, it became apparent that 5-hydroxytryptophan, pyridoxine, and 5-hydroxytryptophan-pyridoxine all raised the levels in blood to an equal degree (Fig 1). The effect of pyridoxine alone was similar to the effect of 5-hydroxytryptophan, and the combination of 5-hydroxytryptophan-pyridoxine was not more effective than each of the individual "medications." There was a gradual decline of 5-hydroxyindole blood levels over time in the treatment groups as well as in the placebo group, although the latter trend was less marked (Table 4 and Fig 1).

In each of the three treatment groups, the effect on total 5-hydroxyindole blood levels was confined to about 40% of the children, whereas the remaining children had mean 5-hydroxyindole blood levels within the range of the placebo group (Table 5). This was not influenced by other conditions, such as congenital heart disease or parental compliance.

Muscle tone examinations done by pediatrician, neurologist, and physical therapist showed a good interexaminer agreement, with an average correlation of 0.55. The examiners observed a gradual increase of muscle tone in children in all of the groups over the study period (Fig 2).

Children who had been randomly assigned to the 5-hydroxytryptophan group initially had higher muscle tone ratings than children in the other two treatment groups and in the placebo group, but the difference was not statistically significant. The slightly increased muscle tone in children from the 5-hydroxytryptophan group as compared with the other three groups continued throughout the study. The muscle tone ratings by the pediatrician during the second and third year of study were noted to be significantly higher in children in the 5-hydroxytryptophan group. However, when children with moderate and severe cardiac disease were excluded, no significant difference was observed among the four study groups (Fig 2).

It has been noted previously that the 5-hydroxyindole blood levels had been elevated in about 40% of the children in the three treatment groups, whereas the remainder of the children in the treatment groups maintained blood levels comparable to the placebo group. Consequently, the 27 children with highest average blood levels were studied to determine whether possible effects of treatment had been confined to these apparent responders.

When the muscle tone analysis was carried out contrasting children with high (> 175 ng/mL) and low (< 175 ng/mL) total 5-hydroxyindole blood levels, no significant difference was noted. In further analyses, the treatment effects were studied for each of 21 measures of cognitive-adaptive function from the Bayley Motor, Bayley Mental, and the Vineland Social

Table 5.—Distribution of Children With Down's Syndrome According to Mean 5-Hydroxyindole Blood Level and Study Group

	5-Hydroxyindole Levels, ng/mL*			
Study Group	**< 135**	**135-175**	**> 175**	**Total**
Placebo	9	8	1	**18**
Pyridoxine	6	10	7	**23**
5-Hydroxytryptophan	6	5	11	**22**
5-Hydroxytryptophan-pyridoxine	7	6	9	**22**
Total	**28**	**29**	**28**	**85†**

Each child was classified according to blood 5-hydroxyindole levels averaged over a period from three to 24 months.
†Four children were not incluced because of insufficient blood data.

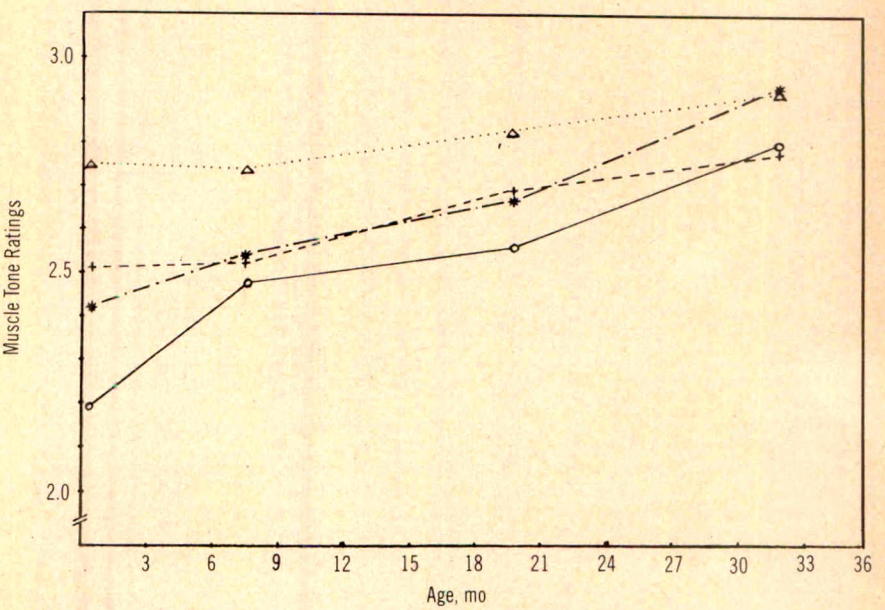

Fig 2.—Mean muscle tone ratings of children with Down's syndrome by age according to study groups. Children with moderate and severe congenital heart disease were omitted. 0 indicates extremely poor muscle tone; 1, markedly increased muscle tone; 2, mildly decreased muscle tone; 3, normal muscle tone; and 4, increased muscle tone. Circles indicate placebo group; crosses, pyridoxine group; triangles, 5-hydroxytryptophan group; and asterisks, 5-hydroxytryptophan-pyridoxine group.

Table 6.—Means, SD, and Interaction Effects of Vineland Social Maturity Scale Raw Scores Obtained at Six-Month Intervals

Age, mo*	Study Group†	Mean	SD	N‡	F	P	Interaction Effect§
6	1	5.7	1.6	12	3.9	.05	−1.4
	2	6.9	.9	18	...	...	...
	3	6.9	.9	20	...	...	...
	4	6.8	1.0	18	...	...	...
12	1	13.2	3.6	10	3.9	.05	−3.3
	2	13.8	2.1	14	...	...	...
	3	15.1	1.8	20	...	...	...
	4	12.4	2.6	20	...	...	...
18	1	18.0	5.0	10	2.8	.05	−4.6
	2	19.5	2.8	14	...	...	...
	3	20.3	2.8	16	...	...	...
	4	17.1	2.5	16	...	...	...
24	1	22.3	5.3	12	1.5	NS	−2.6
	2	23.4	3.8	15	...	...	...
	3	25.3	3.4	19	...	...	...
	4	23.8	3.2	15	...	...	...
30	1	28.3	5.6	13	1.5	NS	−2.3
	2	27.6	3.8	12	...	...	...
	3	30.5	4.5	16	...	...	...
	4	27.5	3.1	15	...	...	...
36	1	32.4	6.4	10	3.4	.05	−3.6
	2	31.5	3.7	15	...	...	...
	3	35.7	3.8	18	...	...	...
	4	31.2	4.5	17	...	...	...

*Children were tested close to the specified times at 6, 12, 18, 24, 30, and 30 months ± 6 days.

†Study group 1 received placebo; study group 2, pyridoxine; study group 3, 5-hydroxytryptophan; study group 4, 5-hydroxytryptophan-pyridoxine.

‡This includes children with mild or no congenital heart disease; the numbers change slightly since not all children always were available for testing.

§Interaction effect equals $mean_1$ minus $mean_2$ minus $mean_3$ plus $mean_4$. The interaction effect measures the extent to which the combined treatment groups had a mean score that differed from what would be expected as a simple additive effect of 5-hydroxytryptophan and pyridoxine alone.

Table 7.—Ratings of Parental Ability to Comply With Furnished Guidance, According to Study Groups

Study Group	Dichotomous Ratings of Parental Compliance*		Total
	Yes	No	
Placebo	8	12	20
Pyridoxine	10	13	23
5-Hydroxytryptophan	17	5	22
5-Hydroxytryptophan-pyridoxine	12	12	24
Total	**47**	**42**	**89**

*$\chi^2 = 7.48$; df 3; $P < .10$.

Maturity Scales at ages 6, 12, 18, 24, 30, and 36 months, and the REEL vocabulary measures at 36 months. There were no statistically significant treatment effects for the Bayley tests or for the REEL examinations at the .05 level when comparing the four study groups. The only findings that were statistically significant occurred on the Vineland Social Maturity Scale at ages 6, 12, 18, and 36 months ($P < .05$) for the overall F test. At 6, 12, and 18 months of age, the source of significant findings was a negative interaction, ie, the children given 5-hydroxytryptophan-pyridoxine performed less well than would have been expected on the basis of 5-hydroxytryptophan and pyridoxine groups. At 36 months of age, the negative interaction on the Vineland Social Maturity Scale was not significant by itself. However, the pattern of effects was the same as at the earlier ages of 6, 12, and 18 months, when there was a slight positive effect of 5-hydroxytryptophan, a slight negative effect of pyridoxine, and negative interaction (Table 6).

Since there is no biochemical basis for expecting or interpreting the negative interaction effect, it was decided to investigate other possible explanations for this peculiar aspect of the data. Subsequently, parental compliance, a nonrandomized variable, was introduced into further analyses. Table 7 gives the compliance data according to study group. While χ^2 analysis did not show a significant difference among the groups ($P > .10$), there is a disproportionate number of "good" compliance cases in the 5-hydroxytryptophan group. Forty-two children whose parents had been less able to comply with furnished guidance were placed in one group and 47 children whose parents carried out recommendations successfully were placed in the other group. There was no evidence of drug effect in the latter group. However, in the former group of children whose parents had difficulties with compliance, the statistically significant negative interaction on the Vineland Social Maturity Scale at ages 6 and 18 months was noted. The group of children whose parents were rated as successful showed consistently higher levels of accomplishment than children in the other group with "poor" compliance, as shown in Table 8. Thus, it seems that if there was any positive drug effect, it was overshadowed by the parental compliance variable. Moreover, analysis of cognitive-adaptive function comparing children with relatively high 5-hydroxyindole blood levels with those of lower 5-hydroxyindole blood levels showed no significant treatment effects.

COMMENT

The failure of past attempts at treatment of children with Down's syndrome are in part due to the complexities and the many unknown elements involved in the pathogenesis of

symptoms and signs in Down's syndrome.

Cognizant of these factors, the rationale of this study was based on the facts that 5-hydroxytryptamine plays an important neurophysiological role as a regulatory amine, that 5-hydroxyindole blood levels are 30% to 50% lower in the newborn child with Down's syndrome, that the 5-hydroxytryptamine concentration can be raised by administration of its precursor 5-hydroxytryptophan, and that 5-hydroxytryptophan administration was reported to increase muscle tone of the child with Down's syndrome. It was hypothesized that the increased muscle tone and enhanced motor activity in children with Down's syndrome receiving 5-hydroxytryptophan would lead to augmented environmental exploration by the child with proportionally greater sensory input, which in turn might be beneficial to his overall development.

As noted in Fig 1, the administration of pyridoxine, hydroxytryptophan, and the combination of 5-hydroxytryptophan-pyridoxine all raised the total 5-hydroxyindole blood level in 40% of the children in the treatment groups. Why did the remaining 60% of the children in the treatment groups not have elevated total 5-hydroxyindole blood levels? Since we made frequent spot checks concerning parental compliance of the administration of the medications, we knew that the vast majority of parents (> 95%) gave the children the medication. Laboratory errors and pharmacy miscalculations as responsible elements for this finding are highly unlikely. Decreased absorption from the intestinal tract may in part account for the low total 5-hydroxyindole blood levels in some children who received the medications.[30] Although some investigators have reported deficiencies in the 5-hydroxyindole pathway (see Fig 3), there is good evidence that this pathway is essentially intact in children with Down's syndrome.[21] It is more likely that failure of 5-hydroxytryptamine uptake, transport, or binding, in addition to limited availability of adenosine triphosphate, may selectively be responsible for the low total 5-hydroxyindole blood concentration in some children of the treatment groups.[31-34] It is also possible that some unidentified metabolic factor made some children respond to the administration of the three compounds in raising 5-hydroxyindole levels, whereas in other children the total 5-hydroxyindole blood levels were not affected by the administration of 5-hydroxytryptophan, pyridoxine, or 5-hydroxytryptophan-pyridoxine.

Table 8.—Bayley Motor and Mental Scales According to the Parental Ability to Comply With Furnished Guidance

Age, mo	Bayley Scales of Infant Development	Ratings of Parental Compliance	Mean	SD	F	P
12	Motor	Yes	8.0	1.5	16.6	.001
		No	6.5	1.3	...	...
	Mental	Yes	7.5	1.7	14.2	.001
		No	6.0	1.3	...	...
24	Motor	Yes	14.9	2.8	14.3	.001
		No	12.1	3.0	...	...
	Mental	Yes	15.1	2.8	32.2	.001
		No	12.0	2.1	...	...
36	Motor	Yes	21.6	4.7	7.9	.02
		No	17.9	4.2	...	...
	Mental	Yes	23.0	4.5	19.1	.001
		No	18.2	3.5	...	...

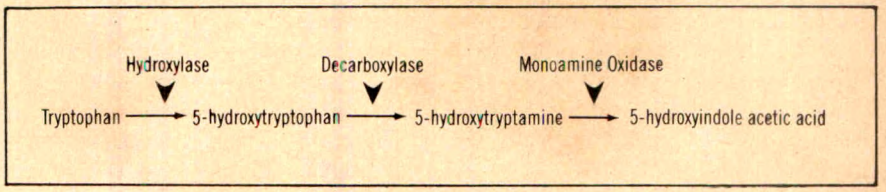

Fig 3.—5-Hydroxyindole pathway.

Compared with Coleman and Steinberg's study,[21] the placebo group in this investigation had higher 5-hydroxyindole blood levels, yet the treatment groups, as noted earlier, had similar total 5-hydroxyindole blood levels as children in Coleman and Steinberg's study who received 5-hydroxytryptophan.[21] They also observed that in some children the 5-hydroxyindole level was significantly raised by 5-hydroxytryptophan administration, whereas in others the 5-hydroxyindole levels were only minimally higher.

It is generally agreed that the conventional assessment of muscle tone is not an accurate science. Therefore, we attempted to objectively quantify the muscle tone of children with Down's syndrome by computerized electromyography; however, these efforts failed. Thus, the examiners assessed the muscle tone in the usual fashion, yet, good correlation was found among the three examiners' individual assessments.

Bazelon et al had initially reported that 5-hydroxytryptophan administration would increase markedly the reduced muscle tone in children with Down's syndrome.[20] In a second study, only a mild increase in muscle tone was noted in children with Down's syndrome who had received 5-hydroxytryptophan during the first few months of life; moreover, after age 4 months, children in the placebo group even tended to have higher muscle tone ratings than children in the treatment group.[21] Similarly, Partington and co-workers as well as Weise and co-investigators, who had administered 5-hydroxytryptophan to children with Down's syndrome, did not find a consistent effect or long-term improvement of muscle tone in their patients.[22,23]

Of primary interest are the results of the cognitive adaptive assessments. A selective, simple analysis of the data could have been interpreted as showing that hydroxytryptophan had

a positive effect enhancing the adaptive function of the child with Down's syndrome, since on the Vineland Social Maturity Scale at 6, 12, 18, and 36 months a statistical significance was found. However, this effect was primarily due to an uninterpretable negative interaction of pyridoxine and 5-hydroxytryptophan. Moreover, when children with moderate and severe cardiac disease were excluded from the analysis and the potential compliance variable was taken into consideration, no significant difference among the children's cognitive-adaptive function was apparent. Although our study has analyzed in much more detail various aspects of the Down's syndrome child's abilities, it is in agreement with previously reported negative results of the administration of 5-hydroxytryptophan to children with Down's syndrome.[21-23]

In an attempt to explain the negative findings in children who were given tryptophan compounds, their known effects on the CNS need to be discussed. It is conceivable that the same defect observed in transport, uptake, and binding of 5-hydroxytryptamine in platelets also exists in the neurons. Although several studies suggested normal synthesis of 5-hydroxytryptamine in the CNS,[35,36] Fellstrom and co-workers reported low levels of 5-hydroxyindoleacetic acid in the CSF of Down's syndrome children.[37] Yet, it is uncertain whether 5-hydroxyindole compounds measured in spinal fluid accurately reflect concentration of 5-hydroxytryptamine at the neuronal level.

No controlled studies are available on 5-hydroxytryptophan and 5-hydroxytryptamine transport across the blood-brain barrier. Even if 5-hydroxytryptophan administered to children with Down's syndrome were transported adequately into the CNS, we still would lack information on how increased 5-hydroxyindole compounds in the CNS would affect the overall mental functioning of these children.

Nonproprietary Names and Trademarks of Drugs

Pyridoxine hydrochloride—*Beadox, Beesix, DBH 86, Hexa-Betalin, Hexavibex.*
Dimethyl sulfoxide—*Dromisol.*

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References

1. Benda CF: *The Child With Mongolism.* New York, Grune & Stratton Inc, 1960.
2. Koch R, Share J, Graliker B: The effects of Cytomel on young children with Down's syndrome (mongolism): A double-blind longitudinal study. *J Pediatr* 66:776-778, 1965.
3. Zimmerman FT, Burgermeister BB, Putnam TJ: Effect of glutamic acid on the intelligence of patients with mongolism. *Arch Neurol Psychiatry* 61:275-287, 1949.
4. Marsh RW, Cabaret JJ: Down's syndrome treated with a low phenylalanine diet: Case report. *NZ Med J* 75:364-365, 1971.
5. Blumberg E: Two years of pituitary treatment in mongoloids: A clinical study. *J Maine Med Assoc* 50:120-125, 1959.
6. Aspillaga MJ, Morizon G, Avendano I: Dimethylsulfoxide therapy in severe retardation in mongoloid children. *Ann NY Acad Sci* 243:421-431, 1975.
7. Schmid F, Haus E, Moradof S, et al: Beeinflussung der mongoloiden Dyszephalie durch Injektionsimplantationen fetaler, heterologer Gehirngewebe. *Fortschr Med* 90:1181-1186, 1972.
8. Oestreicher P: Die Behandlung des Mongolismus. *Monatsschr Kinderheilkd* 121:316-317, 1973.
9. Black DB, Kato JG, Walker GW: A study of improvement in mentally retarded children accruing from sicca cell therapy. *Am J Ment Defic* 70:499-508, 1966.
10. Turkel H: Medical amelioration of Down's syndrome incorporating the orthomolecular approach. *J Orthomol Psychol* 4:102-115, 1975.
11. Share JB: A review of drug treatment for Down syndrome persons. *Am J Ment Defic* 80:388-393, 1976.
12. De la Cruz F: Medical management of mongolism or Down syndrome, in Mittler P (ed): *Research to Practice in Mental Retardation: Education and Training.* Baltimore, University Park Press, 1977, vol 3.
13. Pueschel SM: Therapeutic approaches in Down syndrome, in *Proceedings of Conference on Trisomy 21 (Down syndrome).* Baltimore, University Park Press, to be published.
14. Rosner F, Ong BH, Paine RS, et al: Blood-serotonin activity in trisomic and translocation Down's syndrome. *Lancet* 1:1191-1193, 1965.
15. Tu J, Zellweger H: Blood serotonin deficiency in Down's syndrome. *Lancet* 2:715-716, 1965.
16. Berman JL, Justice P, Hsia DY: The metabolism of 5-hydroxytryptamine (serotonin) in the newborn. *J Pediatr* 67:603-608, 1965.
17. Saxl O: Down's syndrome: New aspects. *Acta Paediatr Acad Sci Hung* 9:329-336, 1968.
18. Bazelon M: Serotonin metabolism in Down syndrome. *Clin Proc Child Hosp DC* 23:58-63, 1967.
19. Carpenter WT: Serotonin now: Clinical implications of inhibiting its synthesis with *p*-chlorophenylalanine. *Ann Intern Med* 73:607-629, 1970.
20. Bazelon M, Paine RS, Cowie VA, et al: Reversal of hypotonia in infants with Down's syndrome by administration of 5-hydroxytryptophan. *Lancet* 1:1130-1133, 1967.
21. Coleman M, Steinberg L: A double-blind trial of 5-hydroxytryptophan in trisomy 21 patients, in Coleman M (ed): *Serotonin in Down's Syndrome.* New York, American Elsevier Publishing Co Inc, 1973.
22. Partington MW, MacDonald MRA, Tu JB: 5-Hydroxytryptophan (5-HTP) in Down's syndrome. *Develop Med Child Neurol* 13:362-372, 1971.
23. Weise P, Koch R, Shaw KNF, et al: The use of 5-HTP in the treatment of Down's syndrome. *Pediatrics* 54:165-168, 1974.
24. Udenfriend S, Weissbach H, Brodie BB, in Glick D (ed): *Methods of Biochemical Analysis.* New York, Wiley-Interscience, 1958, vol 6.
25. Sjoerdsma A, Weissbach H, Terry LL, et al: Further observations on patients with malignant carcinosis. *Am J Med* 23:5-15, 1957.
26. Bayley N: *Manual for the Bayley Scales of Infant Development.* New York, Psychological Cooperation, 1969.
27. Doll EA: *Vineland Social Maturity Scale.* Circle Pines, Minn, American Guidance Service Inc, 1965.
28. Bzoch KR, League R: *The Receptive-Expressive Emergent Language Scale for the Measurement of Language Skills in Infancy.* Gainesville, Fla, The Tree of Life Press, 1970.
29. Pueschel SM, Murphy A: Counseling of parents of infants with Down's syndrome. *Postgrad Med* 58:90-95, 1975.
30. O'Brien D, Groshek A: The abnormality of tryptophan metabolism in children with mongolism. *Arch Dis Child* 37:17-20, 1962.
31. Jerome J, Kamoun P: Diminution du taux de la serotonine associee a un defaut de captation dans les plaquettes sanguines des sujets trisomiques 21. *CR Acad Sci* 264:2072-2075, 1967.
32. Boullin DJ, O'Brien RA: Abnormalities of 5-hydroxytryptamine uptake and binding by blood platelets from children with Down's syndrome. *J Physiol* 212:287-297, 1971.
33. McCoy EE, Bayer SM: Decreased serotonin uptake and ATPase activity in platelets from Down's syndrome patients. *Clin Res* 21:304, 1973.
34. Lott IT, Chase TN, Murphy DL: Down's syndrome: Transport, storage and metabolism of serotonin in blood platelets. *Pediatr Res* 6:730-735, 1972.
35. Dubowitz V, Rogers KJ: 5-Hydroxyindole in the cerebrospinal fluid of infants with Down's syndrome and muscle hypotonia. *Develop Med Child Neurol* 11:730-734, 1969.
36. Tu J, Partington MW: 5-Hydroxyindol levels in the blood and CSF in Down's syndrome, phenylketonuria and severe mental retardation. *Develop Med Child Neurol* 14:457-466, 1972.
37. Fellstrom P, Liedholm M, Lundborg P: Evidence of altered cerebral serotonin metabolism in Down's syndrome from measurements of cerebro-spinal fluid acids. *Pediatr Res* 7:53, 1973.

Mitogenic Response to *Toxocara* Antigen and Chemotactic Defect in Visceral Larva Migrans

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• A 3-year-old girl had the typical features of visceral larva migrans syndrome, including hypereosinophilia, recurrent pulmonary infiltrates, and elevated serum IgG, IgE, and isohemagglutinin titers. A marked mitogenic response of her cultured lymphocytes to *Toxocara* antigen but not to *Ascaris* antigen was found. A neutrophil chemotactic abnormality to *Escherichia coli* culture filtrates and zymosan-activated sera was also demonstrated, which partially corrected after she was treated with diethylcarbamazine citrate.

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Visceral larva migrans (VLM) is a syndrome, occurring primarily in young children, that is characterized by chronic hypereosinophilia, hepatomegaly, hyperglobulinemia, and recurrent transient pulmonary infiltrates.[1] The cause of VLM syndrome appears to be the ingestion of nematode ova and larvae of *Toxocara canis* or *T cati*.[2] Visceral migration of the larvae, which are unable to mature in the human host, is thought to lead to hypersensitivity reactions induced by the foreign proteins. Many children have elevated isohemagglutinin titers and increases in IgE.[3] Intradermal skin tests with *Toxocara* antigen and various serologic tests[2,4] have been unreliable, owing to cross reactions with *Ascaris* and other parasitic antigens. Definitive diagnosis depends on finding larvae in liver or other tissue biopsy specimens.

We have studied a child with typical VLM syndrome who demonstrated a marked mitogenic response to *Toxocara* antigen but not to *Ascaris* antigen. In addition, a chemotactic abnormality of her granulocytes was found. Despite this chemotactic defect, she had no evidence of bacterial infections. After treatment of the VLM syndrome, partial correction of the abnormal chemotaxis was documented.

REPORT OF A CASE

A 3-year-old girl was seen in May 1974 with a temperature of 38.3 °C (101 °F) and pulmonary infiltrates. The WBC count was 22,500 cu/mm, with 59% eosinophils, and the IgE level was 6,410 IU/mL (normal, under 300 IU/mL). The *Toxocara* titers were 1:512 (indirect hemagglutination) and 1:20 (bentonite flocculation); *Ascaris* titers were 1:128 (indirect hemagglutination) and 1:10 (bentonite flocculation). The fever and pulmonary infiltrates cleared spontaneously. There was no family history of recurrent infections or allergies. The patient reportedly had been seen four months earlier with a similar illness. She played outside frequently, but no pica was observed. The family had no pets, but there were numerous dogs and cats in the neighborhood. In February 1975, she was seen for a viral-like illness consisting of malaise, fever, nausea, and vomiting. The WBC count was 11,100/cu mm, with 44% eosinophils. Findings from chest examination were normal, and no hepatosplenomegaly or lymphadenopathy was detected. Skin test results showed positive mumps (+ 12-mm induration) negative purified protein derivative, and negative streptokinase-streptodornase. Quantitation of T and B cells revealed 65% E-rosette-positive and 23% surface immunoglobulin-positive lymphocytes, respectively. Levels of transaminase, serum bilirubin, and alkaline phosphatase were normal. Immunoglobulin levels were as follows: IgG, 2,000 mg/dL (normal, 620 to 1,400 mg/dL); IgE, 17,790 IU/mL (normal, 0 to 300 IU/mL); IgA, 70 mg/dL (normal, 46 to 418 mg/dL); IgM, 144 mg/dL (normal, 70 to 384 mg/dL).

Additional values included total protein, 7.4 g/dL; albumin, 4.2 g/dL; α_1-globulin, 0.2 g/dL; α_2-globulin, 0.8 g/dL; β-globulin, 0.7 g/dL; γ-globulin, 1.5 g/dL. Blood type was 0. Isohemagglutinin (saline) titers were as

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follows: anti-A, 1:4,096; anti-B 1:1,024. The C4 level was 19 mg/dL (normal, 14 to 51 mg/dL); the C3 level was 197 mg/dL (normal, 120 to 185 mg/dL). The illness resolved spontaneously.

In July 1975 *Toxocara* and *Ascaris* titers were negative. The WBC count at that time was 7,400/cu mm, with 33% eosinophils. On Feb 20, 1976, the WBC count was 5,800/cu mm, with 57% eosinophils, and the IgE level was 1,324 IU/mL. Treatment with diethylcarbamazine citrate, 3 mg/kg for 30 days, was begun at that time. In April 1976, the WBC count was 5,600/cu mm, with 9% eosinophils. Since that time, the patient has remained well without recurrence of any symptoms. Repeated WBC and differential cell counts have been normal. Repeated titers in January and April 1977 revealed *Toxocara* titers of 1:64 (indirect hemagglutination) and 1:5 (bentonite flocculation); *Ascaris* titers were undetectable; and IgE titers were 476 and 334 IU/mL, respectively.

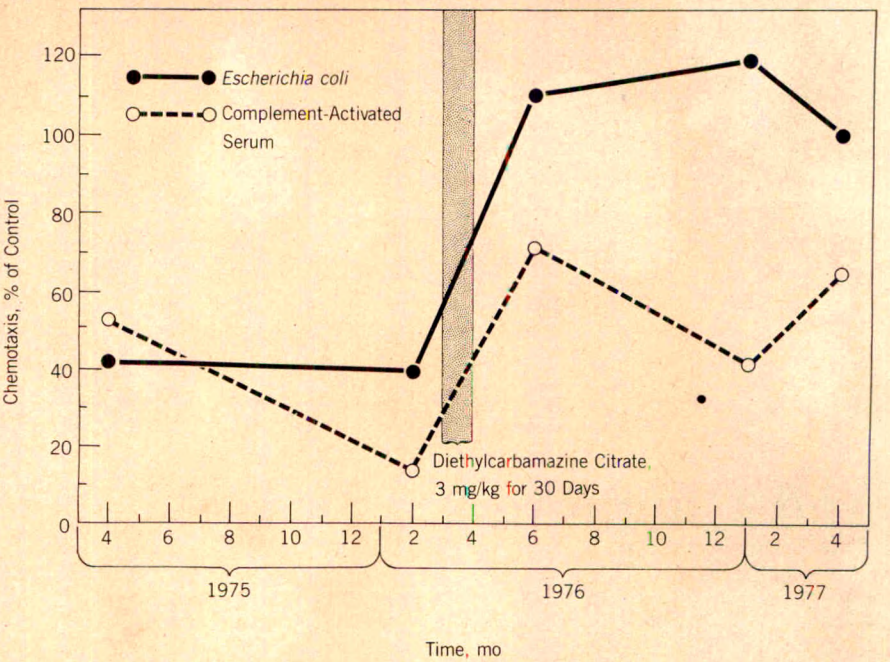
MATERIALS AND METHODS

Chemotaxis was measured by a modification of the Boyden method.[5] Patient and control granulocytes were obtained by dextran sedimentation of heparinized blood. Chemoattractants were filtrates of supernatants from pure cultures of *Escherichia coli* and human control sera in which complement was activated by incubation with zymosan for 30 minutes at 37 °C. Granulocytes and chemoattractants were incubated in chambers separated by 3-μm polycarbonate filters (Millipore) for two hours at 37 °C. Granulocyte suspensions were adjusted to ensure that equal numbers of neutrophils were applied to the filters in all assays. A chemotactic index was derived by dividing the number of neutrophils migrating completely through the filter by the number of neutrophils applied.[6] All assays were done in triplicate.

Lymphocyte transformation assays were performed in triplicate on Ficoll hypaque-separated mononuclear cells obtained from the patient and normal volunteers. Lymphocyte cultures were incubated for 72 hours at 37 °C with dilutions of standard solutions of phytohemagglutinin (PHA), *Toxocara* antigen (0.38 mg of nitrogen per milliliter), *Ascaris* antigen (0.75 mg of nitrogen per milliliter), or no stimulant. Mitogenic response was measured by tritiated thymidine incorporation by scintillation counting.

RESULTS

The results of chemotaxis of patient and control leukocytes to *E coli* filtrates and zymosan-activated sera are shown in the Figure. Prior to treatment with diethylcarbamazine, chemotaxis of the patient's neutrophils to *E coli* or zymosan-activated sera was markedly abnormal compared with normal age-matched control subjects. Following treatment, chemotaxis to *E coli* filtrates became normal. In contrast, chemotaxis to zymosan-activated sera remained abnormal. The patient's serum generated normal chemotactic activity for control neutrophils when exposed to zymosan both before and after diethylcarbamazine therapy.



Chemotactic response of patient neutrophils to *Escherichia coli* filtrates or zymosan-activated normal sera as source of complement expressed as percent of patient chemotactic index compared with control chemotactic index. Multiple same-day control samples gave chemotactic indices within ± 10% of each other on all occasions.

Mitogenic Response to *Toxocara* Antigen

			Ascaris			*Toxocara*		
	Unstimulated	1:100 PHA	25 μg	50 μg	75 μg	19 μg	38 μg	76 μg
Patient, cpm	1,666	138,621	ND*	2,223	828	578,283	592,904	767
Control, cpm	1,951	109,246	1,166	1,418	1,713	ND	998	640

*ND indicates not done.

In the Table, it can be seen that *Toxocara* antigen in concentrations of 19 μg and 38 μg per culture caused a marked mitogenic response in the patient's lymphocytes but none in control subjects. Seventy-six micrograms of *Toxocara* antigen per culture showed no mitogenic response in either patient or control lymphocytes. This concentration may have been toxic to the lymphocytes. *Ascaris* antigen in three different concentrations failed to elicit a mitogenic response in patient or control lymphocytes. The patient and control lymphocytes responded normally to PHA.

COMMENT

This patient demonstrated the typical features of the VLM syndrome—hypereosinophilia, hyperglobulinemia, recurrent pulmonary infiltrates, and elevated isohemagglutinin titers. She also demonstrated markedly elevated levels of IgE, a marked mitogenic response to *Toxocara* antigen, and impaired chemotaxis. Despite abnor-

mal chemotaxis, she had no increased propensity to bacterial infection. The chemotactic abnormality to *E coli* filtrates reversed following treatment of VLM. Concurrently, IgE decreased to near-normal levels and the absolute number of eosinophils became normal. In contrast, chemotaxis to zymosan-activated sera remained abnormal.

Recent investigations have demonstrated a selective in vitro chemotactic defect, which may be elicited by preincubation of normal granulocytes with activated sera as a complement source, while chemotaxis to bacterial chemotaxins remains normal.[7,8] These observations are consistent with the possibility that separate receptors for activated complement and bacterial chemotaxins are present on granulocytes. We believe that our patient may demonstrate this phenomenon. The observation that chemotaxis to *E coli* filtrates returned to normal following treatment but chemotaxis to activated complement remained abnormal suggests that some residual in vivo deactivation of granulocytes to activated complement chemotaxins may remain. In support of this hypothesis, titers to VLM decreased but remained positive, and IgE levels decreased markedly but are still slightly elevated.

The role of IgE as a possible mediator of impaired chemotaxis is unknown.[9] Patients with elevated IgE levels, eosinophilia, recurrent bacterial infections, abnormal cellular immunity, and chemotactic defects have been described.[6,10] While our patient had marked elevation in IgE levels, eosinophilia, and chemotactic defects, she had no increased susceptibility to bacterial infection. Preliminary studies demonstrated that *Toxocara* and *Ascaris* antigens generated chemotactic activity in both the patient's and control sera, but scarce supplies of antigen precluded conclusive studies. Further studies of chemotaxis in patients with VLM syndrome are necessary to confirm our findings.

The definitive diagnosis of VLM syndrome requires the finding of larvae in tissue sections. In an attempt to avoid invasive techniques, various serologic tests[3,4] and intradermal skin tests have been developed. These techniques have lacked both sensitivity and selectivity. Cross-reaction with other parasites, especially *Ascaris*, is the most common problem. The finding of a marked mitogenic response of our patient's lumphocytes to *Toxocara* antigen, but not to *Ascaris* antigen, suggests a promising technique for diagnosing the VLM syndrome. The differentiation of various parasitic infections in patients with hypereosinophilia on the basis of in vitro mitogenic responses may be possible when samples of pure helminth antigens become available.

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Kenneth Walls, MD, Center for Disease Control, Atlanta, supplied the *Toxocara* and *Ascaris* antigens, and Philip Craddock, MD, University of Minnesota, provided technical assistance in the chemotaxis studies.

References

1. Huntley CC, Costas MC, Lyerly A: Visceral larva migrans syndrome: Clinical characteristics and immunodiagnostic studies in 51 patients. *Pediatrics* 36:523-536, 1965.

2. Mok CH: Visceral larva migrans: A discussion based on review of the literature. *Clin Pediatr* 7:565-573, 1968.

3. Hogarth-Scott RS, Johansson SGO, Bennich H: Antibodies to *Toxocara* in the sera of visceral larva migrans patients: The significance of raised levels of IgE. *Clin Exp Immunol* 5:619-625, 1969.

4. Patterson R, Huntley CC, Roberts M, et al: Visceral larva migrans: Immunoglobulins, precipitating antibodies and detection of IgG and IgM antibodies against *Toxocara* antigen. *Am J Trop Med Hyg* 24:465-470, 1975.

5. Boyden SV: The chemotactic effect of mixtures of antibody and antigen on polymorphonuclear leukocytes. *J Exp Med* 115:453-466, 1962.

6. Hill HR, Quie PG: Raised serum-IgE levels and defective neutrophil chemotaxis in three children with eczema and recurrent bacterial infections. *Lancet* 1:183-187, 1974.

7. Bowers TK, Craddock PR, Jacob HS: Acquired granulocyte abnormality during drug allergic reactions: Possible role of complement activation. *Blood* 49:3-8, 1977.

8. Craddock PR, Fehr J, Jacob HS: Complement-mediated granulocyte dysfunction in paroxysmal nocturnal hemoglobinuria. *Blood* 47:931-940, 1976.

9. Fontan G: Defective neutrophil chemotaxis and hyperimmunoglobulinemia E: A reversible defect? *Acta Pediatr Scand* 65:509-511, 1976.

10. Buckley RH, Wray BB, Belmaker EZ: Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics* 49:59-70, 1972.

Partial Trisomy 9q due to Maternal 9/17 Translocation

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• A patient with partial trisomy 9q due to maternal 9/17 translocation was studied and compared with four previously reported cases. The similarity of their clinical features allowed us to delineate a distinct clinical syndrome, which is characterized by psychomotor retardation, dolichocephaly, beaked nose, deep-seated eyes, and long fingers and toes. There is an overlap between some of the features of this syndrome and those of trisomy 9.

(*Am J Dis Child* 134:848-850, 1980)

Trisomy for the distal part of the long arm of chromosome 9 (partial trisomy 9q) has been previously reported in four patients.[1-3] We have studied a fifth patient with this disorder.

REPORT OF A CASE

The patient was born to a 36-year-old gravida 5, para 3, abortus 1 mother at term. There were no antenatal problems, except for two episodes of urinary tract infections. Labor was induced because of decreasing levels of urinary estriols. Fetal distress was noted during labor, with episodes of tachycardia, bradycardia, and meconium staining of the amniotic fluid. The Apgar scores were 4 and 7 at 1 and 5 minutes of life, respectively. The birth weight was 1,810 g, the birth length was 45.5 cm, and the head circumference was 33 cm.

Examination demonstrated several dysmorphic features, which prompted a karyotype analysis. The baby fed poorly and failed to thrive. She was able to follow objects by 2 months of age, but at age 5½ months she did not smile or vocalize. She was not able to lift her head or roll over. Examination at 5½ months of age (Fig 1 through 3) revealed the following values: weight, 4.2 kg; length 60 cm; and head circumference, 42.2 cm.

There was obvious dolichocephaly. The nose was long, fleshy, and slightly beaked, with hypoplastic alae nasae. The eyes were deep-seated. The mouth was small, well designed, and triangular, and there was a narrow, high-arched palate. The chin was small and receding. The ears were relatively large and square, with abnormal folding of the tragus. The neck was short, with redundant skin folds posteriorly. The trunk was asymmetric, the right side being more prominent, and the right nipple was larger than the left.

There were bilateral sacral dimples, as well as elbow dimples. The extremities were thin, and the fingers and toes were unusually long and thin. The fingers were held in flexion, and were clutched over the thumb. There was an extra volar crease on both index fingers at the level of the middle phalanx. Dermatoglyphics were unremarkable. There was nonpitting edema of the dorsum of the feet. The clitoris and labia minora were hypoplastic. There was severe limitation to hip abduction, and some limitation to knee extension.

She had a weak, hoarse cry. The tone was poor. She had stereotyped writhing movements of the arms and legs in an avoidance manner.

A roentgenogram showed the long bones to be unusually long and slender. There were 13 pairs of ribs. The cranial tables were thin, with discrete cortical margins and minimal diploë. The EEG and ECG were normal.

Fig 1.—Full view of patient with trisomy 9q, demonstrating facies, dolichocephaly, slender extremities, and long fingers and toes.

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Reprints not available.

Fig 2.—Facies of patient with trisomy 9q. Note long fleshy nose, well-designed triangular mouth, and relatively large ears.

Fig 3.—Hand of patient with trisomy 9q, showing long fingers flexed and clutched over thumb.

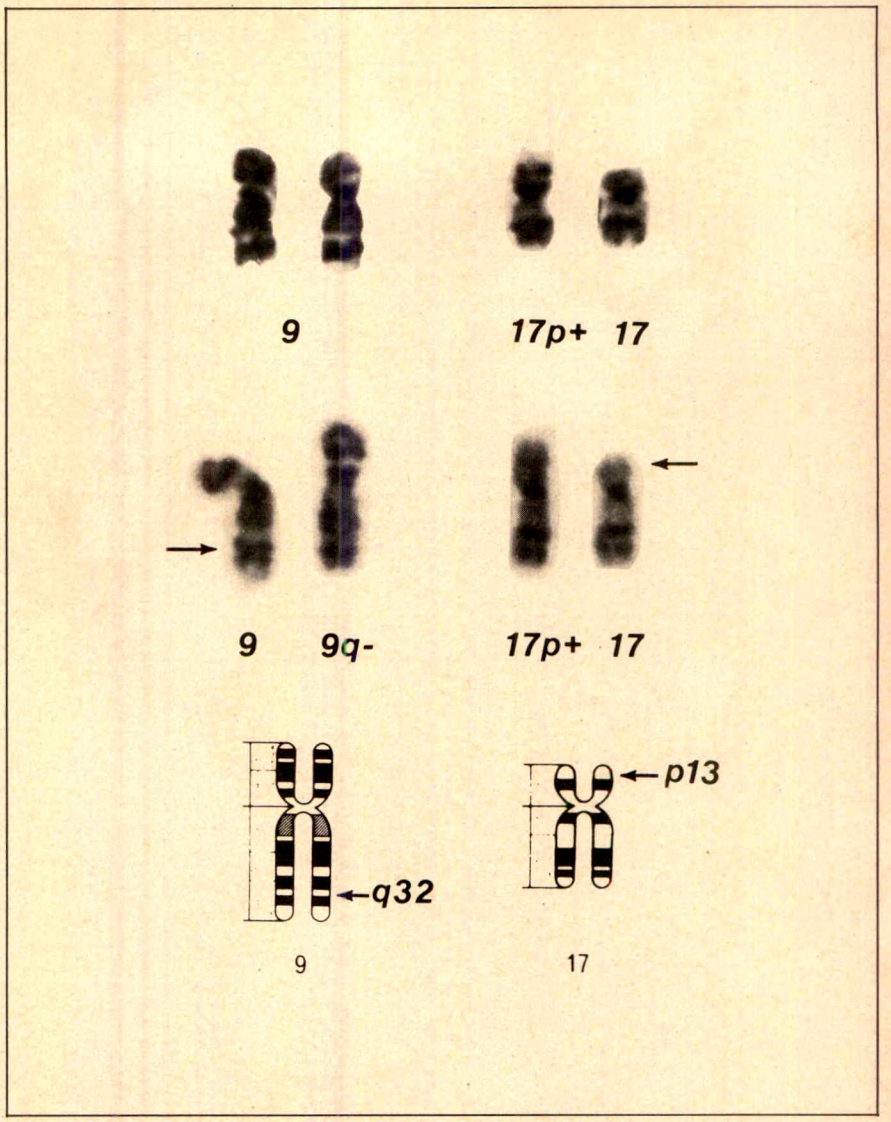

Fig 4.—Partial karyotypes showing pairs 9 and 17 (DNA replication banding) from the patient with trisomy 9q32→qter, 46,XX,der(17), t(9;17) (q32;p13)MAT (top), mother with balanced 9/17 translocation, 46,XX,t(9;17) (arrows show breakpoints in relation to normal chromosome of pair) (middle), and illustration of breakpoints (bottom). Because chromosome pictures are from DNA replication-banded preparations, banding patterns are similar, but not identical, to those obtained after standard Giemsa banding.[6] In particular, proximal region of long arm of chromosome 9 shows dark banding not seen in Giemsa-banded preparation. Pattern on rest of chromosome 9 long arm is same as that obtained after Giemsa banding.

Chromosome preparations were made from lymphocyte cultures grown in the presence of 10 μg/mL of 5-bromodeoxyuridine and pulsed with thymidine for the last six hours before harvesting. These were then stained with DNA-specific fluorescent stain 33258 (Hoechst), exposed to sunlight, incubated in a solution of 0.3M sodium chloride and 0.03M trisodium citrate at 60 °C and stained with Giemsa stain to produce DNA-replication bands.[4,5]

Analysis of such preparations from the patient demonstrated a 46,XX,17p+ karyotype (Fig 4). The abnormal chromosome 17 was inherited from her mother, who was found to carry a balanced translocation t(9;17) (q32;p13) (Fig 4). The patient is therefore trisomic for the region 9q32→9qter.

COMMENT

Several cases of trisomy for the short arm of chromosome 9 (trisomy 9p) have allowed the delineation of a specific chromosomal syndrome.[7,8] The main features of this syndrome include mental retardation, microcephaly, prominent forehead, hypertelorism, enophthalmus, prominent nose, hypoplastic phalanges and nails, clinodactyly, absence of the C triradius, and simian creases. A number of cases have been described of either complete trisomy 9 or trisomy 9 involving the short arm and a variable length of the proximal portion of the long arm.[9-13] The clinical features included most of those of 9p trisomy, with additional features that were variable, depending on the length of

Clinical Features of Partial Trisomy 9q in Five Patients					
	Source				
	Turleau et al[1] Patient 1	Turleau et al[1] Patient 2	Subrt et al[2]	Faed et al[3]	Present Case
Low birth weight	+	–	–	+	+
Severe physical and mental retardation	+	+	+	+	+
Stereotyped movements of extremities	+	+	...	...	+
Dolichocephaly	+	+	+	–	+
Deep-seated eyes	+	+	+	–	+
Prominent beaked nose	+	+	+	+	+
Small, well-designed mouth	+	+	–	+	+
Microretrognathia	+	+	+	+	+
Relatively large ears	–	+	+	–	+
Short neck with redundant skin	–	–	+	–	+
Long fingers and toes	+	+	+	+	+
Flexion of fingers	+	+	+	–	+
Limited joint movements	–	–	+	+	+
Congenital heart disease	–	–	+	–	–
Hypoplastic external genitalia	–	–	–	+	+
Unremarkable dermatoglyphics	+	+	+	+	+

the segment of the long arm involved in the trisomy. The most important additional features included cranial suture abnormalities, urogenital anomalies, congenital heart malformations, articular malformations, failure to thrive, and early death.

Four patients with trisomy that affected only the distal portion of the long arm of chromosome 9 (partial trisomy 9q) have been reported with comparable features strikingly similar to those described in the present case. The characteristic features are summarized in the Table. Most striking among those are severe psychomotor retardation, craniofacial dysmorphic features, and long fingers and toes. An important negative finding is the lack of dermatoglyphic abnormalities.

Some features of patients with partial trisomy 9q, such as low birth weight and failure to thrive, overlap with those of trisomy 9. Furthermore, limitation of joint movements in three cases, the hypoplastic external genitalia in two cases, and the congenital heart disease in one case, have been described in some of the patients with trisomy 9. In spite of the described similarities, the overall appearance of those patients with partial trisomy 9q permits them to be identified as having a separate syndrome with a characteristic phenotype.

The clinical features of this syndrome will be better delineated as more cases are described. To our knowledge, this is the first case reported in a pediatrics journal, and it is hoped that it will alert pediatricians to this distinct chromosomal syndrome.

References

1. Turleau C, de Grouchy J, Chavin-Colin F, et al: Partial trisomy 9q: A new syndrome. *Hum Genet* 29:2?3-242, 1975.
2. Subrt I, Janovsky M, Jodl J: Partial trisomy 9q: Chromosomal syndrome. *Hum Genet* 34:151-154, 1976.
3. Faed M, Robertson J, Brown S, et al: Pure partial trisomy for long arm of chromosome 9. *J Med Genet* 13:239-242, 1976.
4. Hoo JJ, Parslow MI, Chambers D: Combination of differential sister chromatid staining, G-banding pattern and X-inactivation pattern. *Hum Genet* 47:291-295, 1979.
5. Latt SA: Microfluorometric detection of deoxyribonucleic acid replication in human metaphase chromosomes. *Proc Natl Acad Sci* 70:3395-3399, 1973.
6. Kandra PM, Ray M: Analysis of DNA replication patterns of human fibroblast chromosomes: The replication map. *Hum Genet* 43:139-149, 1978.
7. Rethoré MO, Larget-Piet L, Abonyi D, et al: Sur quatre cas de trisomie pour le bras court du chromosome 9: Individualisation d'une nouvelle entité morbide. *Ann Génét* 13:217-232, 1970.
8. Podruch PE, Weisskopf B: Trisomy for the short arms of chromosome 9 in two generations, with balanced translocations t(15p+;9q–) in three generations. *J Pediatr* 85:92-95, 1974.
9. Haslam RHA, Broske SP, Moore CM, et al: Trisomy 9 mosaicism with multiple congenital anomalies. *J Med Genet* 10:180-184, 1973.
10. Feingold M, Atkins L: A case of Trisomy 9. *J Med Genet* 10:184-187, 1973.
11. Bowen P, Ying KL, Chung GSH: Trisomy 9 mosaicism in a newborn infant with multiple malformations. *J Pediatr* 85:95-97, 1974.
12. Sutherland GR, Carter RF, Morris LL: Partial and complete Trisomy 9: Delineation of a Trisomy 9 syndrome. *Hum Genet* 32:133-140, 1976.
13. Mace SE, Macintyre NN, Turk KB, et al: The Trisomy 9 syndrome: Multiple congenital anomalies and unusual pathological findings. *J Pediatr* 92:446-448, 1978.

Acquired Bile Duct Stricture in Childhood Related to Blunt Trauma

Report of a Case and Review of the Literature

Ross S. Kendall, MD; Paul R. Chapoy, MD; Ronald W. Busuttil, MD, PhD; Marvin Kolodny, MD; Marvin E. Ament, MD

• A 13-year-old boy had obstructive jaundice following several episodes of blunt abdominal trauma. At surgery, a stricture of the common bile duct, for which no other cause could be found, was identified and corrected. We describe our approach to the problem of obstructive jaundice in childhood. In most cases, the application of ultrasonography or computerized tomography and appropriate transhepatic cholangiography can yield a presumptive diagnosis before surgical exploration.

(*Am J Dis Child* 134:851-854, 1980)

Blunt abdominal trauma resulting from assault or automobile accidents poses an increasingly common dilemma to many surgeons. Patients who had suffered massive injuries and shock are usually surgically explored, yet inadvertent injury without immediate signs and symptoms can manifest as late unrecognized sequelae. We recently encountered an uncommon case of obstructive jaundice in childhood, probably due to blunt injury to the common bile duct. Physicians who care for children should be aware that mild, blunt abdominal trauma, with injury to the common bile duct, may be a cause of obstructive jaundice after infancy.

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REPORT OF A CASE

On Jan 29, 1979, a 13-year-old boy was transferred from another hospital with a ten-day history of epigastric abdominal pain, nausea, nonbilious vomiting, acholic stools, dark urine, and jaundice. The pain was described as intermittent, crampy, lasting one to two hours, and radiating to the back; it was unrelated to meals, position, or exercise. A history of fever, diarrhea, constipation, melena, rectal bleeding, and hematemesis was denied.

The patient had been well until August 1978, when he experienced similar pain, without jaundice or vomiting, for one month subsequent to several episodes of blunt abdominal trauma. A helmet injury to the upper part of the abdomen had sent him to the sidelines in a football game. The following day, a football hitting the abdomen reproduced excruciating pain. He continued to experience abdominal discomfort thereafter, and lost 5.5 kg, although he did not relate his symptoms to his football trauma. He experienced no change in stool habits. An upper gastrointestinal (GI) tract x-ray series and endoscopy disclosed no pathologic features. After one month of symptoms, he remained asymptomatic from September 1978 to January 1979. A family history of cholelithiasis in the mother, peptic ulcer disease in one grandmother, and a fatal "strangulation of a Meckel's diverticulum" in a sibling was reported.

Our physical examination in January 1979 revealed an obese mildly icteric adolescent in no acute distress. His weight was 60.4 kg and height was 160 cm. Blood pressure was 130/85 mm Hg, pulse rate was 95 beats per minute, respirations were 26/min, and temperature was 37 °C. His stools were pale and without occult blood. Urine was dark and tested positive for bile. There were no physical stigmas of chronic liver disease. He had diffuse right upper quadrant and epigastric tenderness, with marked guarding and no rebound pain. Bowel sounds were diminished. There were no palpable masses or organomegaly, and liver span measured 11 cm by percussion. No bruits were heard over the abdomen. Laboratory values included the following: total serum bilirubin/direct fraction, 5.4 mg/dL/4.5 mg/dL (normal, 1.0 mg/dL); serum alkaline phosphatase, 590 to 735 IU/L (normal, 10 to 45 IU/L); SGOT, 279 IU/L (normal, 6 to 36 IU/L); SGPT, 945 IU/L (normal, 10 to 45 IU/L); 5′ nucleotidase, 20.9 mu/mL (normal, 15 mu/mL); and antistreptolysin O titer, 500 Todd units (normal, 120 Todd units). Normal values were obtained for serum amylase, amylase-creatinine clearance ratio, total serum proteins, albumin, electrolytes, BUN, creatinine, cholesterol, triglycerides, blood hemo-

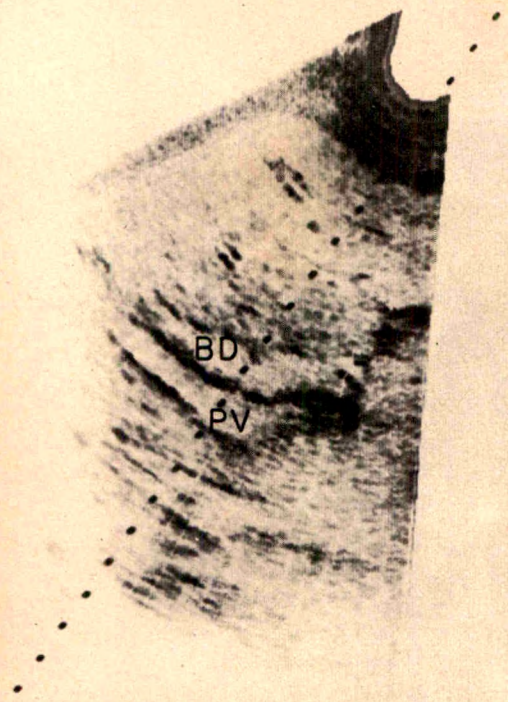

Fig 1.—Ultrasound study. Longitudinal section of liver showing dilated intrahepatic duct structure ("shotgun sign"): portal vein (PV); bile duct (BD).

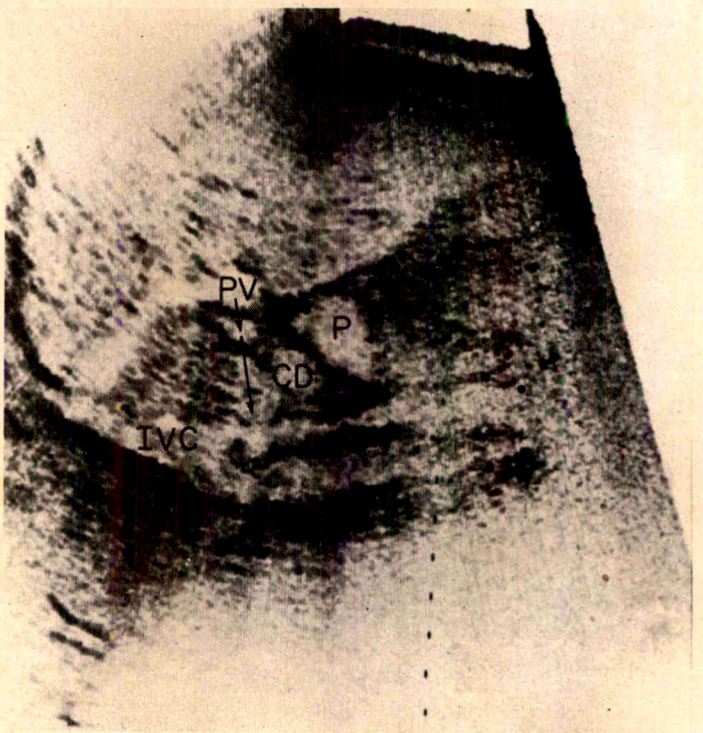

Fig 2.—Ultrasound study. Longitudinal section showing dilated common bile duct: common bile duct (CD); inferior vena cava (IVC); pancreas (P); portal vein (PV).

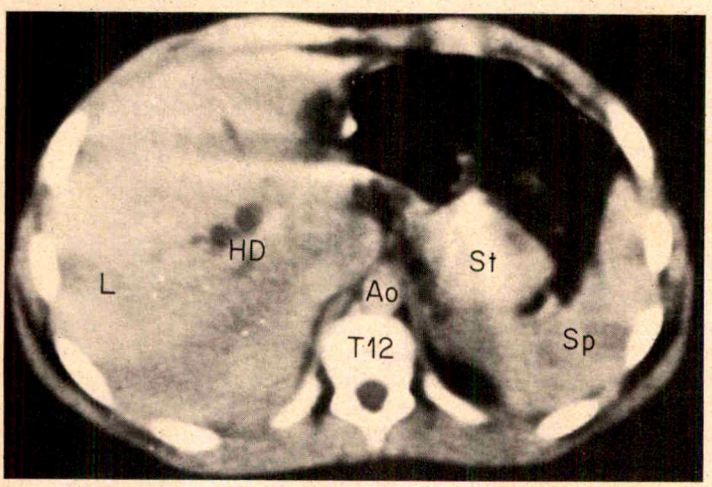

Fig 3.—Computerized tomographic scan showing dilation of branches of hepatic duct at level of T12: aorta (Ao); liver (L); division of hepatic duct (HD); spleen (Sp); stomach (St).

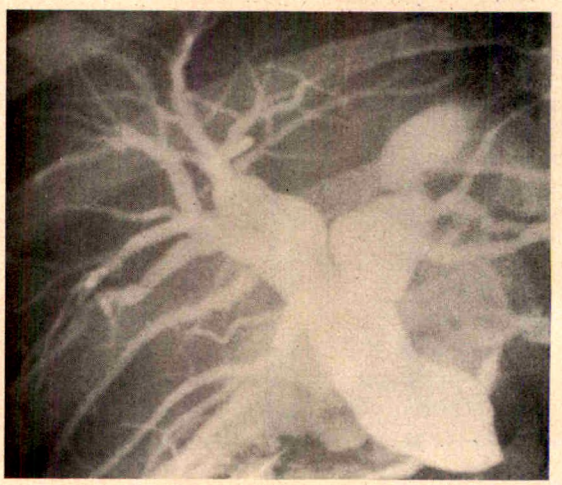

Fig 4.—Transhepatic cholangiogram showing common bile duct stricture.

globin, hematocrit, WBC count and differential cell count, and prothrombin time.

An abdominal ultrasound examination demonstrated dilated bile ducts ("shotgun sign")[1] and a dilated cystic structure at the level of the common bile duct (Fig 1 and 2). The liver appeared normal; pancreatic echoes were obscured by bowel gas, and the gallbladder was not identified. Abdominal computerized tomography (CT) confirmed dilation of the bile duct (Fig 3). A transhepatic cholangiogram revealed total extrahepatic obstruction of the biliary tract at the middle third of the common bile duct, with dilation proximally to a diameter of 1.5 to 2.0 cm (Fig 4).

Exploratory laparotomy was performed four days after admission. At surgery, a fibrous mass encasing a strictured distal common bile duct was identified. After ruling out malignancy (by frozen section), a Roux-en-Y diversion was performed with resection of the involved common duct and fibrous mass, cholecystectomy, choledochojejunostomy, jejunojejunostomy, and needle biopsy of the liver. The gallbladder was contracted with gross and microscopic evidence of chronic inflammation; there were no gallstones. The common duct was strictured and there was evidence of chronic inflammation and extravasation of bile into surrounding fibrous tissue (Fig 5 and 6). The liver showed minimal perportal

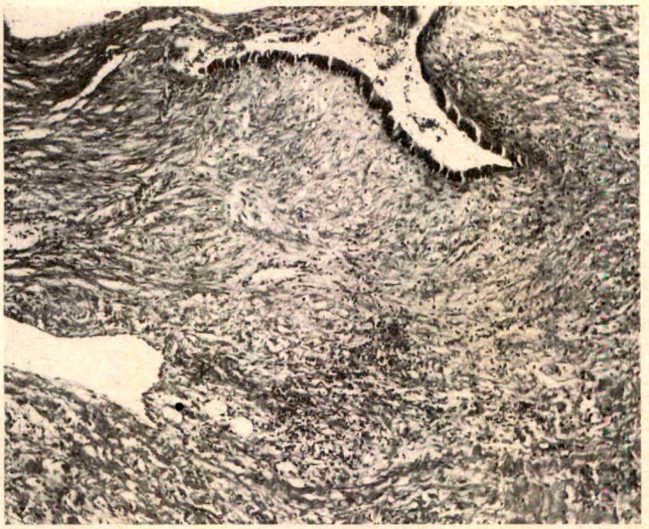

Fig 5.—Common bile duct shows chronic inflammation and fibrosis above stricture (hematoxylin-eosin, original magnification ×64).

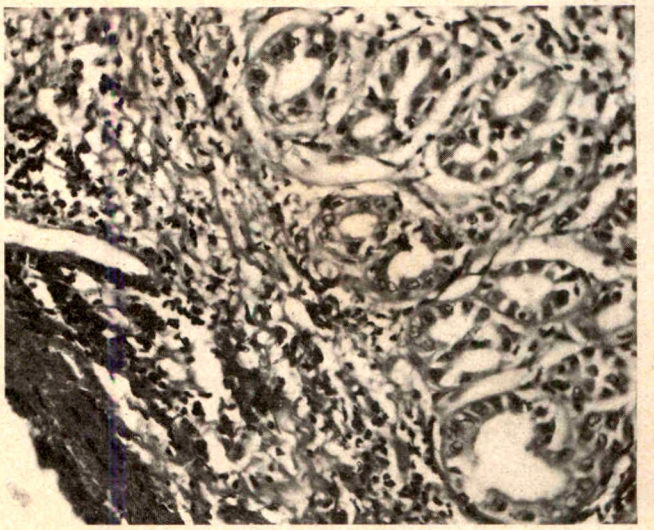

Fig 6.—Common bile duct shows proliferating bile duct structures. There is mild inflammation and fibrosis at site of stricture (hematoxylin-eosin, original magnification ×205).

inflammation and bile duct proliferation. There was no evidence of a malignant neoplasm in tissue submitted from the gallbladder, liver, common duct, duodenum, or sentinel lymph nodes. There were no microabscesses in the wall of the common duct to suggest cholangitis, nor were there hemosiderin-laden macrophages to suggest resolved hematoma. No extravasated bile lakes were seen outside the duct lumen.

The patient made a rapid recovery. Bile obtained at transhepatic cholangiography and surgery proved to be sterile. Patency of the biliary tree was demonstrated radiographically one week after operation. Liver function has since returned to normal and the patient remains clinically well 11 months after hospital discharge.

COMMENT

Isolated blunt injury to the extrahepatic ducts occurs rarely in children and adults. In one adult series[2] of 43 patients with nonsurgical trauma to the extrahepatic bile ducts, only six had suffered injury to other major organs. Such figures are representative of other large studies of the problem.[2-4] Among the ten cases reported by Fletcher et al,[4] only three involved children and all were toddlers. A recent review of the literature[5] uncovered only 33 cases of nonpenetrating injury to the bile ducts in children since 1916, most of which were part of massive multiple trauma patterns secondary to battering or automobile accidents. Moreover, in only six of these was the injury to the common bile duct isolated and incomplete enough to manifest with long-delayed sequelae, namely, biliary obstruction. The site of injury was usually at the pancreatic-duodenal junction. The other site of ductal injury was at the bifurcation of the hepatic duct or the origin of the left hepatic duct, and involved hepatic trauma as well. It is known that shearing forces cause tearing at points of maximum fixation, occurring in the biliary tree at the point of exit from the porta hepatis and entry into the pancreas. The common bile duct is shorter and more fixed than the accompanying artery or vein, so that it can be individually injured. One case of blunt injury to the midcommon duct in a 19-month-old child has been reported.[6]

Bile duct strictures causing obstructive jaundice are very rarely seen in pediatric patients. Cholestatic jaundice may be classified as intrahepatic or extrahepatic. After infancy, in the United States and Europe the predominant sources of extrahepatic obstructive jaundice are (1) obstruction to the intrapancreatic portion of the common bile duct from inflammation (pancreatitis) or pancreatic pseudocyst (traumatic or postinflammatory), (2) choledochal cyst or other congenital anomalies, (3) cholelithiasis, and (4) cholangitis. In underdeveloped countries, parasites such as *Ascaris*, *Clinorcis sinenses*, *Fasciola hepatica*, and, occasionally, *Echinococcus* produce extrahepatic biliary obstruction. Strictures, which are rare, can be congenital, malignant, or inflammatory in origin. Inflammatory strictures can be secondary to cholangitis (infection, "pancreatic reflux") or trauma.

Although many authors state that stricture of the common bile duct usually follows surgical complications of cholecystectomy,[7-11] the rate of stricture following such surgery is less than 1%. In Warren and Jefferson's review of 987 patients with bile stricture seen during a 25-year period at the Lahey Clinic, 97% occurred after surgery.[10] Of the 29 cases (3%) in which surgery could not be implicated, 15 were inflammatory (ie, secondary to documented cholangitis), five were congenital, seven were secondary to gallstones, and only two developed from blunt external trauma.

Proof of a cause-and-effect relationship between the trauma and stricture was, as in our patient, circumstantial. In cases of complete transection with bile peritonitis,[12] the relationship is clear. However, in our case, congenital and infectious causes must be eliminated by the history (onset in adolescence subsequent to lack of fever, without recurrent obstruction after 11 months), findings of laboratory tests (sterile bile cultures), and the pathologic features

(absence of microabscesses in the wall of the common duct, absence of gallstones). Several authors have recently argued that a continuum of bile duct injury, from stricture or perforatior to choledochal cyst, may stem from pancreatic reflux into a congenitally deformed pancreaticobiliary junction.[13,14] In the past, spontaneous perforation of bile ducts, a well-documented occurrence only in the neonate,[15] has been ascribed to increased intraluminal pressure on areas of the duct weakened by a congenital anomaly or prenatal infarction of the wall. Whether congenital bile strictures are secondary to sublethal variations of these complications or result from failure to recanalize during embryogenesis is unknown. Our patient is beyond the age when a congenital bile duct stricture could develop.

We used the accepted radiologic approaches used in adults to examine our patient: ultrasonography, CT scan, and percutaneous transhepatic cholangiography. Many authors have debated the advantages and disadvantages of ultrasonography vs CT scan in the investigation of possible obstructive jaundice and delineation of the biliary tree.[1,16-19] Both studies demonstrated the problem clearly in our patient. There are no good published series on the use of ultrasonography vs CT in the diagnosis of childhood jaundice. Ultrasound is the preferred scanning method over CT scan in our facility because of lower costs and a skilled ultrasonography department. The efficacy and safety of transhepatic cholangiography in defining biliary obstruction have been well shown in adults[20,21]; however, no large series has been published on its use in children. It has been successfully used in infants,[22] and we are now employing it without difficulty in most children in whom the cause of obstructive jaundice has not clearly been demonstrated by noninvasive means.

The surgical approach to nonmalignant disruption or obstruction of the distal common bile duct has been well reviewed by several authors.[10,23-26] Several approaches, including direct anastomosis over a T-tube stint, choledochojejunostomy, Roux-Y cholecystojejunostomy, Roux-Y choledochojejunostomy, and choledochogastrostomy, are used. Most surgeons now perform the repair procedure used in our patient, a Roux-Y choledochojejunostomy. A discussion of the various procedures is beyond the scope of this presentation.

CONCLUSION

This case probably represents a distinctly unusual injury resulting from blunt abdominal trauma in childhood. To our knowledge, it is only the seventh such case reported in the pediatric age group. Although it is a rare cause of cholestatic jaundice in childhood, a history of trauma should be sought in puzzling cases of biliary obstruction. This case demonstrates that diagnostic tools available for the investigation of obstructive jaundice in adult patients are also valuable in pediatric diagnosis.

References

1. Weill F, Eisencher A, Zeitner F: Ultrasonic study of the normal and dilated biliary tree: The 'shotgun sign.' *Radiology* 127:221-224, 1978.
2. Haynes DC: Non-surgical trauma to the extrahepatic bile ducts. *South Med J* 62:1323-1326, 1969.
3. Lee JG, Wherry DC: Traumatic rupture of the extrahepatic biliary ducts from external trauma. *J Trauma* 1:105-114, 1961.
4. Fletcher WS, Mahnke DE, Dunphy JE: Complete division of the common bile duct due to blunt trauma. *J Trauma* 1:87-95, 1961.
5. Ahmed S: Bile duct injuries from non-penetrating abdominal trauma in childhood. *Aust NZ J Surg* 46:209-212, 1976.
6. Waldhausen JA, King H: Traumatic rupture of the bile ducts. *J Indiana State Med Assoc* 56:1107-1109, 1963.
7. McCallister AJ: Biliary stricture. *Am J Surg* 132:567-571, 1976.
8. Glenn F: Iatrogenic injuries to the biliary ductal system. *Surg Gynecol Obstet* 146:430-434, 1978.
9. Warren KW, Braasch J: Common bile duct stricture: Prevention and repair. *Surg Clin North Am* 45:617-630, 1965.
10. Warren KW, Jefferson M: Prevention and repair of strictures of the extrahepatic bile ducts. *Surg Clin North Am* 45:617-630, 1965.
11. Way LW, Dunphy JE: Biliary stricture. *Am J Surg* 123:287, 1972.
12. Gould L, Patel A: Ultrasound detection of extrahepatic encapsulated bile, 'biloma.' *Am J Roentgenol* 132:1014-1015, 1979.
13. Babbit OP: Congenital choledochal cysts: A new etiologic concept based on anomalous relationship of the common bile duct and pancreatic bulb. *Ann Radiol* 12:231, 1969.
14. Okhawa T, Okuyama T: A malformation of the pancreato-biliary system as a cause of perforation of the biliary tract in childhood. *J Pediatr Surg* 12:541-547, 1977.
15. Fitzgerald RJ, Parbho K, Guiney EJ: Spontaneous perforation of bile ducts in neonates. *Surgery* 83:303-305, 1978.
16. Goldberg HI, Filhy RA, Korobkin M, et al: Capability of CT body scanning and ultrasonography to demonstrate the status of biliary ductal system in patients with jaundice. *Radiology* 129:731-737, 1978.
17. Havrilla TR, Haaga JR, Alfidi RJ, et al: Computed tomography and obstructive biliary disease. *Am J Roentgenol* 128:765, 1977.
18. Malini S, Sobel J: Ultrasonography in obstructive jaundice. *Radiology* 123:429-433, 1977.
19. Morris AI, Fawcett RA, Wood R, et al: Computerized ultrasonography in cholestatic jaundice. *Gut* 19:685-688, 1978.
20. Burcharth F, Christiansen L, Efsen F, et al: Percutaneous transhepatic cholangiography in the diagnostic evaluation of 160 jaundiced patients. *Am J Surg* 133:559-561, 1977.
21. Cooperberg P, Ayre-Smith G, Garrow DG: Grey scale ultrasound of biliary tract disease: A correlative study with percutaneous transhepatic cholangiography. *J Can Assoc Radiol* 28:237-242, 1977.
22. Nelson R, Hamlyn AN, Lavelle I: Fine needle percutaneous transhepatic cholangiography in the investigation of cholestasis in infancy. *J Pediatr Surg* 12:727-728, 1977.
23. Pickelman JR: Biliary tract surgery. *Surg Clin North Am* 57:1221-1234, 1977.
24. Warren KW: Management of strictures of the biliary tract. *Surg Clin North Am* 51:3, 1971.
25. Wheeler ES, Longmire WP Jr: Repair of benign stricture of common bile duct by jejunal interposition choledochoduodenostomy. *Surg Gynecol Obstet* 146:260-262, 1978.
26. Williams GR: Experiences with surgical reconstruction of the hepatic ducts. *Ann Surg* 179:540, 1974.

Intracranial Hemorrhage in the Premature

Its Predictive Features and Outcome

Niki Kosmetatos, MD; Colleen Dinter, MD; Margaret L. Williams, MD; Herbert Lourie, MD; Alfred S. Berne, MD

• **Sixty-four infants with birth weights of 500 to 1,500 g were studied to determine the incidence and outcome of intracranial hemorrhage. Thirty-seven (58%) had hemorrhage and of these 60% died. Of the survivors, progressive hydrocephalus requiring treatment developed in only two infants. Serial computerized tomographic scans with measurement of ventricular-brain width ratios were found to be useful in objectively evaluating hydrocephalus. Review of perinatal data showed no association of maternal or obstetrical factors with neonatal hemorrhage but the infants who had intracranial bleeding showed a high incidence of low Apgar scores, respiratory distress syndrome, acidosis, hypoxia, apnea, hypotension, seizures, and requirement for respiratory support. Multiple regression analysis of potentially causative factors assigned importance to low gestational age, respiratory distress syndrome, birth asphyxia (low Apgar score), and vaginal delivery.**

(*Am J Dis Child* 134:855-859, 1980)

With progressive improvement in respiratory support of the preterm infant, an increasingly recognized cause of death has been intracranial hemorrhage.[1-5] Numerous studies on the cause and timing of such hemorrhages and their relationship to the respiratory distress syndrome, hypoxia, hyperosmolarity, and clotting deficits have been undertaken.[6-11]

Until recently, the antemortem diagnosis of intracranial hemorrhage has been made by indirect means, such as evaluation of clinical signs and examination of spinal fluid, which has made study of incidence and interpretation of associated factors difficult and possibly inaccurate. The advent of computerized axial tomography (CT) offers for the first time the opportunity to make positive antemortem diagnoses and to follow the natural history of this disease.[12-16] Computerized tomographic scanning also allows the clinician to observe the development of hydrocephalus and to evaluate objectively the efficiency of varying therapeutic regimens.

The following report of experience with intracranial hemorrhage measures incidence, describes clinical course, and attempts to delineate the antecedents of hemorrhage in a high-risk population—the infant who weighs less than 1,500 g at birth.

MATERIALS AND METHODS

All infants of birth weight 1,500 g or less, either inborn or transported, admitted to the Special Care Nursery at Crouse Irving Memorial Hospital in Syracuse, NY, from Feb 1, 1978 through Sept 31, 1978 were entered into the study. Infants clinically suspected of having had an intracranial hemorrhage were scanned by CT as soon as the clinical condition permitted; all other infants were scanned at 7 to 10 days of age. Surviving infants in whom hemorrhage had been demonstrated were followed up weekly for four weeks by CT scanning to observe for progressive ventricular dilation. If an infant died prior to CT scanning, every attempt was made to obtain an autopsy or to perform intraventricular taps to establish the diagnosis of intraventricular hemorrhage.

Data collected on each pregnancy included maternal age, parity, underlying illness, medications, complications of pregnancy, and expected date of confinement. Delivery history as to the time of rupture of membranes, duration of labor, presence of fetal distress, mode of delivery, presentation, anesthesia, and Apgar scores was ascertained where possible and resuscitative measures were recorded. Weight, height, and head circumference were entered on standard growth charts. Physical, neurological, and Dubowitz examinations were performed on the infants. Vital signs, including blood pressure, daily weights, daily fluid intake, weekly head circumference, blood glucose determinations with glucose oxidase paper strips (Dextrostix), as well as sex, race, and birth order were recorded for all infants. Maternal menstrual history, Dubowitz examination results, and intrauterine growth data were used to estimate gestational age.

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Assays of serum sodium, potassium, calcium, bilirubin, capillary or venous hemoglobin, arterial or capillary blood pH, P_{CO_2}, and P_{O_2}, and spinal fluid were obtained when indicated. Respiratory support information was recorded.

The CT scanning was performed in the Department of Radiology with the use of a head scanner. A one-minute scan time was used. Sedation was not necessary and thermal and respiratory support and cardiac monitoring were provided as necessary. One of us (A.S.B.), a radiologist, reviewed all CT scans.

Once the presence of hemorrhage was established, an attempt was made to determine extent and location. Hemorrhages were divided into four groups based on location: subarachnoid only, subependymal, intraventricular (IVH), and parenchymal plus IVH. As an objective measurement of ventricular dilation, a ventricular width-brain width (V/B) ratio was determined in the plane of the head of the caudate nucleus. After reviewing CT scans in the infants who had no hemorrhage, a V/B ratio of less than or equal to 0.2 was considered normal. Any ratio greater than 0.2 was considered to represent ventricular dilation. This measurement was also used to follow the progression of dilation on serial CT scans.

The presence of respiratory distress syndrome was determined by clinical and laboratory evidence consistent with the diagnosis in the presence of a compatible chest roentgenogram. Other causes of respiratory distress, such as transient tachypnea of the newborn, pneumonia, and aspirations, were considered as a separate category. All roentgenograms were reviewed without knowledge of the clinical diagnosis or the presence of hemorrhage. Arterial or capillary blood samples were obtained in 57 of 64 babies. Hypercarbia was defined as a P_{CO_2} above 50 mm Hg, acidosis as a pH less than 7.20, and hypoxia as a P_{aO_2} of less than 50 mm Hg, a capillary P_{O_2} of less than 35 mm Hg, or clinical cyanosis. Only those determinations made in the first 48 hours of life were included in the analysis as insufficient data are available on well infants and infants who died to allow comparison with the hemorrhage group after this period.

In the evaluation of apnea, episodes were considered as present when the infant's respiratory monitor was triggered after a 15-s delay and the infant was found to be without respiratory effort. Only episodes that occurred in the first 48 hours of life and required either stimulation or other intervention were considered. Apnea developed in only one infant in the first week of life after the first 48 hours. Apneic episodes developed in this infant on day 6 and the infant was diagnosed as having necrotizing enterocolitis. Since this infant did not have an intracranial hemorrhage on CT evaluation and the apnea could be related to another cause, analysis of apnea as a variable was confined to the first 48 hours.

Total intake of all fluids, including blood products, medications and "intravenous flushes" as well as intravenous and oral maintenance was determined for the first and second day of life. Infants were divided into two groups for statistical analysis: those with intakes less than 150 mL/kg/day and those with intakes greater than or equal to 150 mL/kg/day. Hypernatremia was defined as a serum sodium level greater than or equal to 150 mEq/L, hyponatremia as less than or equal to 130 mEq/L. A blood glucose determination with glucose oxidase paper strips in the first 48 hours of life greater than 130 mg/dL was considered hyperglycemia.

Significance of individual observations was computed by Student's t test or χ^2 test with Yates' correction. A stepwise multiple regression analysis was performed on the data relevant to the cause of hemorrhage.

RESULTS

Seventy infants with birth weights between 500 and 1,500 g were entered in the study. Six infants died before any evaluation could be performed, and autopsy permission was denied. These six infants ranged between 510 and 1,330 g (mean, 890 g) and between 23 and 37 weeks' gestation (mean, 27.8 weeks). They did not differ in historical, clinical, or laboratory data from the remainder of the infants and were excluded from further evaluation.

Of the remaining 64 infants, 37 were found to have intracranial hemorrhage, an incidence of 58%. Diagnosis was made at autopsy for seven cases, by postmortem ventricular taps for three, and by CT scan for the remainder. The characteristics of the entire population are given in Table 1. The infants with hemorrhage had significantly lower gestational ages and birth weights than those without hemorrhage, but otherwise the groups were similar.

Table 2 gives the outcome of the two groups with regard to survival, presence of initial ventricular dilation, and subsequent progress of the dilation. Twenty-two of the 37 infants with hemorrhage died, whereas all but two of the 27 infants without hemorrhage survived. Infants with subarachnoid hemorrhage only or subependymal hemorrhage that had not extended to the ventricles had a lower mortality than those with ventricular and parenchymal involvement. Although initial ventricular dilation was seen in 16 of the 27 infants with hemorrhage who had CT scans, progressive hydrocephalus requiring the placement of a shunt developed in only two. The others showed stable or regressing ventricular size by the second to third week on CT evaluation.

Historical, clinical, and laboratory data were analyzed to determine predictors of hemorrhage. No association was demonstrated between hemorrhage and any maternal historical information, complications of pregnancy, fetal presentation, duration of labor, and presence of fetal distress. With respect to the infant, the development of hemorrhage was associated by χ^2 analysis, with low Apgar score, need for ventilation in the delivery room, subsequent development of respiratory distress syndrome, metabolic acidosis, hypoxia, apnea, hypotension, seizures, and requirement of respiratory support, either constant positive airway pressure or ventilator (Table 3). Infants with hemorrhage received

Table 1.—Population Characteristics

	Hemorrhage	No Hemorrhage
Total No. of patients	37	27
Mean birth weight, g (range)	1,038 (670-1,445)*	1,248 (822-1,500)*
Mean estimated gestational age, wk (range)	28.4 (24-35)*	30.9 (27-39)*
Appropriate for gestational age (%)	35 (95)	21 (78)
M (%)	26 (70)	13 (48)
W (%)	34 (92)	23 (85)
Transported (%)	18 (49)	8 (30)

*Significant difference, $P < .001$, by Student's t test. Other differences nonsignificant by χ^2 test with Yates' correction.

Table 2.—Outcome of Infants

	Total	Survived	Died
Without hemorrhage	27	25	2
With hemorrhage*			
Survival based on location of hemorrhage			
Subarachnoid only	2	2	0
Subependymal without IVH	6	4	2
Intraventricular	19	6	13
Parenchymal + IVH	10	3	7
Survival based on initial ventricular size by CT			
V/B ≥ 0.2	16	5	11
V/B ≤ 0.2	11	10	1
No estimate (diagnosed by other means)	10	0	10
Subsequent course of surviving infants with IVH			
Blood cleared (no residual dilation)	10	10	0
Stable or regressing dilation (V/B > 0.2 < 0.6)	4	4	0
Progressive hydrocephalus (V/B ≥ 0.6)	2	1	1
Total	**37**	**15**	**22**

*IVH indicates intraventricular hemorrhage and V/B, ventricular-brain width ratio.

Table 3.—Clinical Data Predictive of Intracranial Hemorrhage

	Hemorrhage (N = 37)	No Hemorrhage (N = 27)	P*
Apgar score ≤ 4 at 1 min	25	8	< .01
Ventilation in delivery room	24	6	< .001
Respiratory distress syndrome	25	4	< .001
pH ≤ 7.2 in first 48 hr	27	7	< .001
Base deficit ≥ 10 mEq/L	25/34	6/22	< .001
Pao_2 < 50 mm Hg; Po_2 (capacity) < 35 mm Hg	27/36	6/24	< .001
Apnea in first 48 hr	28	11	< .01
Hypotension in first 48 hr	25	9	< .01
Seizures	12	0	< .001
Ventilator	26	4	< .001
Fluid intake > 150 mL/kg/day-48 hr	19/27	10/26	< .05

*Significance by χ^2 test.

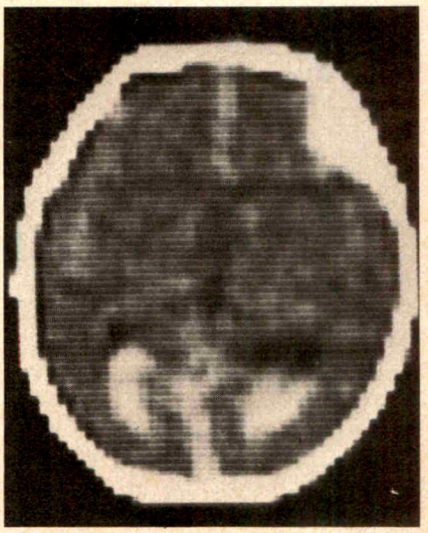


Fig 3.—Computerized axial tomography demonstrating bilateral intraventricular and subarachnoid hemorrhage with mild initial ventricular dilation.

Fig 4.—Follow-up computerized axial tomography on same infant at four weeks with complete resolution of blood and ventricular dilation.

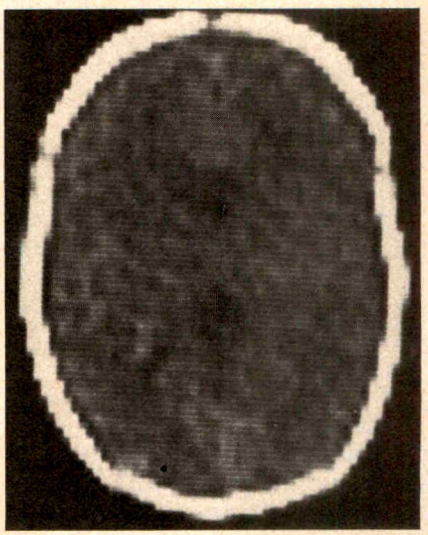


Fig 1.—Computerized axial tomography demonstrating bilateral intraventricular, subependymal, and subarachnoid hemorrhage in infant. Initial ventricular dilation was noted.

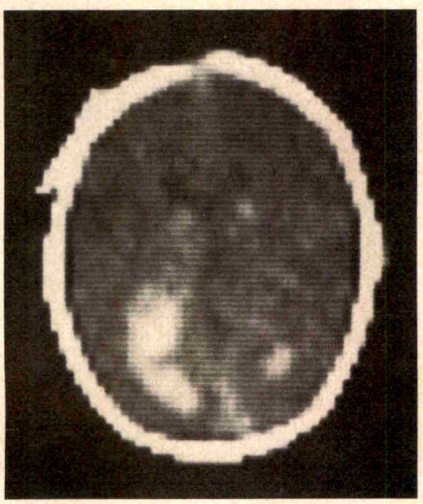
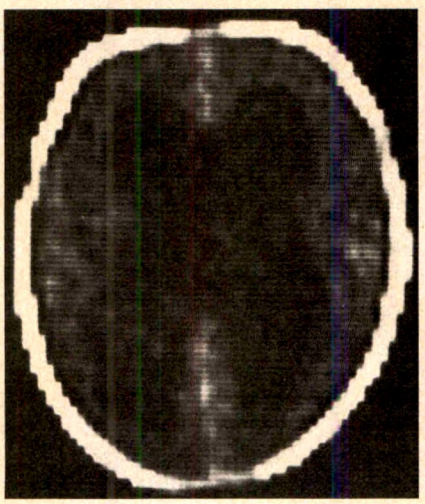


Fig 2.—Same infant four weeks later progressing to hydrocephalus.



somewhat greater fluid intakes on the first day of life than those with no hemorrhage. No association of intracranial bleeding with hypothermia, hypernatremia, hyponatremia, hypercarbia, or hyperglycemia was noted.

Several of the factors examined have been suggested as possibly causative as well as symptomatic of intracranial hemorrhage. Since the majority are interrelated, a stepwise multiple regression analysis was performed of variables that might have causal importance. The most significant independent contributions to the variability ($P < .001$) were made by low gestational age and presence of the respiratory distress syndrome. Other significant independently related variables ($P < .01$) included low Apgar score (as a measure of intrauterine insult), the presence of respiratory distress from other causes than respiratory distress syndrome, and vaginal delivery as opposed to cesarean section. Seven of 18 infants delivered by cesarean section had intraventricular hemorrhage, compared with 30 of 46 infants delivered vaginally. Acidosis, hypoxia, hypercarbia, and hypotension did not appear to play a role when examined by multiple regression analysis. The difference in results may be due to the interrelation of these factors with respiratory distress syndrome and birth asphyxia. Birthweight, sex, and hypothermia also did not appear to play a role in the development of intracranial hemorrhage on regression analysis.

Seizures developed in 12 infants in the hemorrhage group and none in the nonhemorrhage group. The development of seizures in the low-birthweight sick infant suggested the diagnosis of intracranial hemorrhage clinically. However, the absence of seizures did not exclude the diagnosis since 25 of the 37 infants with hemorrhage had no seizure activity. The 12 infants with seizures had more severe hemorrhages: five had extensive hemorrhages with parenchymal involvement and seven had intraventricular hemorrhages without parenchymal extensions. The absence of seizures, however, did not necessarily indicate milder hemorrhages since 18 of these infants had intraventricular hemorrhages (two with parenchymal involvement). Bulging fontanelles were found in only eight infants with hemorrhages and six of these had seizures. Decreases in hematocrit levels were not useful indicators of hemorrhage since multiple blood drawings and transfusions made interpretation of hematocrit values difficult. Twenty-one of the 37 infants with hemorrhage had no clinical indications and diagnosis was made by CT or at postmortem.

As with diagnosis, only the presence of seizures correlated with the clinical course and site of hemorrhage. Infants with seizures had the most extensive hemorrhages often with parenchymal involvement, and the highest mortality: only one of the 12 survived; progressive hydrocephalus developed in that infant (Fig 1 and 2). By comparison, 14 of the 25 infants without seizures survived. Table 2 gives the survival of infants with hemorrhages based on the location of hemorrhage and initial ventricular dilation.

COMMENT

Intracranial hemorrhage is an important cause of neonatal mortality and morbidity in the low-birth-weight infant. Until recently, the diagnosis was made by postmortem examination or inferred from physical signs, symptoms, and laboratory data. Using these variables, an almost uniformally fatal outcome was assumed. Recent studies indicate that such is not the case and also suggest a higher incidence of neonatal hemorrhage than previously suspected since all hemorrhages do not necessarily result in symptoms.[16-17]

Using CT, Papile et al[16] found an incidence of intracranial hemorrhage of 43% in infants of birth weight less than 1,500 g and demonstrated that 45% of these infants survived the hemorrhage. Even more surprising was their finding that 78% of surviving infants with documented hemorrhage had no clinical findings consistent with intracranial bleeding. This study served to illustrate that the incidence of intracranial hemorrhage when diagnosed by clinical signs alone is probably underestimated, and that prognosis for surviving infants may be better than previously assumed.

Our data support these conclusions. In the present study, the incidence of hemorrhage was 58%; and 40% of these infants survived compared with 92% survival in the nonhemorrhage group. More importantly, the short-term outcome of these infants was remarkably good. All except one infant had no evidence of gross blood by CT scan at nine to ten days after the hemorrhage. Progressive ventricular dilation developed in only two children requiring shunting procedures; in the other children who had initial dilation, ventricular size stabilized or decreased by the end of the month (Fig 3 and 4). This is a lower incidence of hydrocephalus than has previously been reported in surviving infants. Ventricular dilation was more common with extensive intraventrical hemorrhage with or without parenchymal extension as opposed to subependymal or mild hemorrhage. However, as most infants with extensive hemorrhages did not survive, the question of how many infants with such hemorrhages, if surviving, would go on to have progressive ventricular dilation remains unanswered. In only one of the two infants with progressive dilation would the clinical course and site of hemorrhage have been helpful. The other infant had a moderate hemorrhage without parenchymal involvement and mild initial ventricular dilation. It is apparent that a spectrum of disease occurs and in larger series it is possible that correlation of clinical presentation with initial CT evaluation may provide useful objective criteria for predicting outcome.

The V/B ratio was used as an objective measure of ventricular size. An attempt was made to establish criteria of "normality" in infants without hemorrhage, and serial measurements were used to follow the progress of ventricular dilation in individual infants. In view of finding that ventricular size will stabilize or decrease in most infants after hemorrhage, it is important to follow this measurement objectively for a period of time prior to initiating treatment. These data can also serve as a baseline in evaluating the results of varying therapeutic

regimens, such as repeated lumbar puncture,[18-19] glycerol[20] or isosorbide administration,[21] or shunting procedures.

With the improved potential of accurate diagnosis by CT scan, it is now increasingly possible to identify risk factors associated with hemorrhage. Symptoms, such as apnea, hypotension, and acidosis, occur so regularly with intracranial bleeding that their appearance in a small premature infant is very suggestive that hemorrhage may be occurring. Difficulty persists however in distinguishing causal factors from events occurring as a result of the hemorrhage. Regression analysis suggests that many of the associated findings represent related effects of the hemorrhage that do not independently influence the occurrence of the bleeding. Hypotension for example was a frequent concomitant of hemorrhage but did not seem to have an independent causative role, a fact not supportive of the recent suggestion of Lou et al[22] that the impaired autoregulation of cerebral blood flow in distressed newborn infants might allow hypotension to be a factor in the cause of hemorrhage. Analysis of possible causative factors related hemorrhage most strongly to immaturity and to the presence of hyaline membrane disease irrespective of hypoxia. It is possible, however, that the latter association may represent a common causation for the two diseases as opposed to damage to the cerebral circulation resulting from some facet of the pulmonary disease.

Another factor identified as independently important was the mode of delivery. A large number of the infants in whom intracranial bleeding did not develop had been delivered by cesarean section, whereas most of those who had hemorrhage were born vaginally. Passage of the soft head of a premature infant through the birth canal increases the potential for both depression of cerebral blood flow and cerebral trauma. Although the data suggest that cesarean section may offer protection against intracranial hemorrhage, further documentation of this fact should be sought before it is used as a basis for recommendation of surgical delivery for all small premature infants.

The very low-birth-weight infant should be considered at risk for intracranial bleeding that now can be diagnosed by CT scan. However, the as-yet unproved safety in terms of radiation exposure to the retina prompts restriction of its use to only those infants who are at high risk and to the minimum exposure necessary to obtain the information. Until further delineation of the relationship of symptoms to outcome, the infants in whom hemorrhage is identified must continue to be considered at maximum risk for later neurological, developmental, and behavioral problems.

The present study was approved of by the Human Research Review Committee of Crouse Irving Memorial Hospital.

References

1. Gruenwald P: Subependymal cerebral hemorrhage in premature infants and its relation to various injurious influences at birth. *Am J Obstet Gynecol* 61:1285-1292, 1951.
2. Fedrick J, Butler NR: Certain causes of neonatal death: II. Intraventricular hemorrhage. *Biol Neonate* 15:257-290, 1970.
3. Ross JJ, Dimmette RML: Subependymal cerebral hemorrhage in infancy. *Am J Dis Child* 110:531-542, 1965.
4. Towbin A: Cerebral intraventricular hemorrhage and subependymal matrix infarction in the fetus and premature newborn. *Am J Pathol* 52:121-139, 1968.
5. Tsiantos A, Victorin L, Relier JP, et al: Intracranial hemorrhage in the prematurely born infant. *J Pediatr* 85:854-859, 1974.
6. Dyer NC, Brill AB, Tsiantos AK, et al: Timing of intracranial bleeding in newborn infants. *J Nucl Med* 14:807-811, 1973.
7. Harrison VC, de V Heese H, Klein M: Intracranial haemorrhage associated with hyaline membrane disease. *Arch Dis Child* 43:116-120, 1968.
8. Simmons MA, Adcock EW, Bard H, et al: Hypernatremia and intracranial hemorrhage in neonates. *N Engl J Med* 291:6-10, 1974.
9. Thomas DB: Hyperosmolarity and intraventricular haemorrhage in premature babies. *Acta Pediatr Scand* 65:429-432, 1976.
10. Gray OP, Ackerman A, Fraser AJ: Intracranial haemorrhage and clotting defects in low-birth-weight infants. *Lancet* 1:545-548, 1968.
11. Papile L, Burstein J, Burstein R, et al: Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. *J Pediatr* 93:834-841, 1978.
12. Butzer JF, Cancilla PA, Cornell SH: Computerized axial tomography of intracerebral hematoma. *Arch Neurol* 33:206-214, 1976.
13. Krishnamoorthy KS, Fernandez RA, Momose KD, et al: Evaluation of neonatal intracranial hemorrhage by computerized tomography. *Pediatrics* 59:165-172, 1977.
14. McCullough DC, Kufta C, Axelbaum SP, et al: Computerized axial tomography in clinical pediatrics. *Pediatrics* 59:173-181, 1977.
15. Scott WR, New PFJ, Davis KR, et al: Computerized axial tomography of intracerebral and intraventricular hemorrhage. *Radiology* 112:73-80, 1974.
16. Papile L, Burstein J, Burstein R, et al: Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 grams. *J Pediatr* 92:529-534, 1978.
17. Deonna T, Payot M, Probst A, et al: Neonatal intracranial hemorrhage in premature infants. *Pediatrics* 56:1056-1064, 1975.
18. Goldstein GW, Chaplin ER, Maitland J, et al: Transient hydrocephalus in premature infants: Treatment by lumbar puncture. *Lancet* 1:512-514, 1976.
19. Papile LA, Koffler H, Burstein R, et al: Nonsurgical treatment of acquired hydrocephalus: evaluation of serial lumbar puncture. *Abst Pediatr Res* 12:554, 1978.
20. Volpe JJ: Neonatal intracranial hemorrhage: Pathophysiology, neuropathology, and clinical features. *Clin Perinatol* 4:77-99, 1977.
21. Lorber J: Isosorbide in treatment of infantile hydrocephalus. *Arch Dis Child* 50:431-436, 1975.
22. Lou HC, Lassen NA, Friis-Hansen B: Impaired autoregulation of cerebral blood flow in distressed neonates. *J Pediatr* 94:118-121, 1979.

Pregnancy, Delivery, and Neonatal Complications Among Autistic Children

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• **An investigation of the prenatal, delivery, and neonatal experience of 145 autistic children matched with 330 unaffected siblings revealed that among the propositi there was a preponderance of first-born children. Obstetrical records, which had been made prior to the diagnosis of autism, indicated that autistic children were more likely than their siblings to have experienced at least one untoward event during their mothers' gestations and deliveries. Similarly, the autistic children had an increased risk of neonatal complications. Despite the significant excess of total reproductive complications in the autistic series, there was no single event or a combination of biologically related complications that could reasonably account for any large number of cases of autism. While it is possible that autism may be the product of several diverse deleterious events experienced in utero, during delivery, or in the early neonatal period, our finding could be a chance occurrence or could signal the presence of an unknown factor responsible both for autism and for a variety of reproductive complications.**

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The symptomatology and clinical course of autism suggest that physical damage to the brain or nervous system may play a role in the etiology of this disorder.[1-3] High frequencies of electroencephalographic (EEG) abnormalities,[4,5] seizure disorders,[6-8] and cognitive deficiencies[9,10] among autistic children may indicate a nonspecific neurologic involvement. Since a variety of reproductive complications are associated with fetal neurologic impairment, we have examined the role of selected obstetric, delivery, and neonatal difficulties as possible contributors to the development of autism.

As part of a study evaluating a possible association between prenatal or early infancy viral exposure and the subsequent development of autism, a series of 183 autistic children and 355 unaffected siblings was assembled, and prenatal, delivery, and early neonatal medical data obtained.[11] In this report we compare the frequency of prenatal and delivery complications and early medical difficulties for the autistic children and their nonautistic siblings.

SUBJECTS AND METHODS

The Sample

The subjects for this investigation consisted of 145 autistic children and 330 unaffected siblings, a subsample of the larger study.[11] Twenty of the original 183 autistic children were excluded because they had no siblings for comparison. An additional 18 cases belonging to nine individual sibships were excluded from the study because the propositi came from families with more than one autistic child. Sibships with more than one autistic child were excluded because the matched analysis was designed to evaluate the frequency of the selected reproductive complications among the propositi relative to normal siblings within each sibship. Inclusion of sibships with two autistic children would have necessitated the use of the same comparison subjects twice.

Cases were referred to us between June 1975 and January 1977 by 19 agencies in Massachusetts known to evaluate, treat, educate, or care for children with autism or related disorders. The referral sources included psychiatric and neurologic clinics, in-patient psychiatric units, evaluation centers at schools for the retarded, and special day and residential schools. With the exception of two referral sources that were primarily diagnostic and referral centers, all agencies referred children who were currently under their care. The two diagnostic centers referred children evaluated in the preceding 12 months but who were not undergoing diagnostic procedures at the time of the study. To protect confidentiality, the agencies' directors wrote to parents describing the study as an investigation of childhood developmental difficulties. The names of families who expressed a willingness to participate were given to us for further contact.

A subject's inclusion in the study was determined by the history of manifest symptomatology rather than by the diagnosis of autism. Subjects were potentially eligible for study inclusion if by age 6 they had exhibited one or more symptoms in at least one of the three areas described subsequently. Children with manifest impairment in all three areas were classified as totally or classically autistic; those with a history of impairment in only one or two areas were classified as partially autistic. In the total sample of 183 autistic children, 132 (72%) showed impairment in all three areas by age 6; 44 (24%) showed impairment in two of the three areas; and seven (4%) showed impairment in only one area. Among the subsample of 145 children included in this study, 125 (86%) were totally autistic. Because of the small number of children with fewer than three impaired areas, totally and partially autistic subjects were combined.

The 19 participating medical and educational facilities referred children whose clinical record contained a notation of impairment in at least one of the three specified areas. Confirmation of the symptoms was obtained by an interview with the subjects' parents. Only seven subjects who had been referred failed to meet study inclusion criteria either because the onset of symptoms occurred after age 6 or because their symptomatology did not represent any of the three areas of impairment. It seems clear that the referral

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sources correctly identified a large proportion of subjects eligible for study inclusion. Unfortunately, we are not able to assess the number of potential study subjects who were not referred.

Symptom Areas

The three general areas that were considered criteria for autism were (1) impaired relatedness to the environment, characterized by (*a*) extreme aloneness, lack of responsiveness to human contact, no interest in people, and apparent emotional self-sufficiency, (*b*) physical withdrawal from people, stiffening when held, pushing people away, and a preference for isolation, (*c*) avoidance of eye to eye contact, and (*d*) treatment of persons as inanimate objects; (2) stereopathy, characterized by (*a*) repetitive acts, play, or behavior, (*b*) insistence on sameness in routine and environment, (*c*) self-stimulation (head banging, compulsive masturbation, repetitive scratching, or picking at skin), (*d*) rigid food preferences and aversions, and (*e*) rote memory; and (3) impaired language development, characterized by (*a*) mutism (no spoken language), (*b*) echolalia (parroting the speech of others, use of third person rather than first person pronouns), (*c*) communicative speech limited to a few words, and (*d*) aberrant inflection.

Data Collection

Data on pregnancy, delivery, and neonatal complications were obtained by interviewing the subjects' mothers and by reviewing all available obstetrical and delivery records. Medical records were found for 118 of the 145 propositi (81%) and for 246 of the 355 unaffected siblings (75%).

To minimize observation bias, a research assistant, who was unaware of which child in the sibship was the propositus, abstracted the medical records. While data have been collected from both sources (medical records and family interview), we have, in this analysis, used only medical record data for the assessment of complications during pregnancy and delivery. However, for events in the early postnatal phase, data from the interviews were used, since the obstetrical records rarely contain information beyond the delivery phase. To evaluate whether the data provided by the subjects' mothers could be considered reasonably accurate and unbiased, we compared the information on pregnancy and delivery difficulties obtained from the mothers with that found in the medical records. In addition, we also determined the proportion of complications reported by the families that were substantiated by the medical records and the proportion of medically reported events confirmed by the maternal interviews, both for propositi and for the comparison group of siblings. Estimates of risk of pregnancy and delivery complications obtained from interview data were very similar to those obtained from medical data only. The proportion of family-reported complications confirmed by medical records and the proportion of record data confirmed by family interviews were comparable for propositi and siblings. The results of these comparisons indicate that family-provided data are consistent with those found in medical records. There was no evidence that the mothers preferentially recalled medical events for either propositus or siblings.

Methods of Analysis

Since the comparison subjects were the unaffected siblings of the propositi, the propositi and the comparison subjects were matched on a variety of genetic and environmental factors. The data were therefore subjected to a matched analysis designed to accommodate propositi with a variable number of comparison subjects.[12] Factors that might confound the association between reproductive complications and autism were controlled for in the analysis.

RESULTS

Among the autistic children there were almost 4.5 times as many males as females (118 vs 27). Among the siblings the number of males and females were roughly equal (163 and 167, respectively).

Birth Order

As shown in Table 1, there was an excess of first-born and a deficit of second-born among the propositi. Table 2 gives the distribution of autistic children by birth order and sibship size. The expected number of autistic children in each birth order was estimated by the Greenwood-Yule method,[13] which presupposes completed sibships. When some sibships are still incomplete, as is the case in this sample, the Greenwood-Yule method will produce an over-representation of propositi in the later birth orders. The data in Table 2, reflecting the observed and expected birth order distribution of autistic cases by sibship size, indicate that the excess of autistic children in the first birth order is evident only in small sibships, whereas the deficit of cases in the second birth order is present in sibships of all sizes. The observed excess of cases in birth orders 5 and above is possibly due to the bias just mentioned and cannot be construed to indicate an excess risk for children who are the youngest of several siblings. The difference between the observed and expected distribution of cases by birth order tested by χ^2 for homogeneity is significant at $P < .001$.

Table 1.—Birth Order of Propositi and Siblings

Birth Order	Propositi		Siblings	
	No.	%	No.	%
1	66	45.5	80	24.2
2	26	17.9	119	36.1
3	26	17.9	66	20.0
4	15	10.3	34	10.3
5	8	5.6	17	5.2
6+	4	2.8	14	4.2
Total	**145**	**100.0**	**330**	**100.0**

Table 2.—Birth Order and Sibship Size for Propositi*

Sibship Size	Birth Order						Total
	1	2	3	4	5	6+	
2	40 26.5	13 26.5	... ...	... ...	... ...	... ...	53
3	17 14.3	11 14.3	15 14.3	... ...	... ...	... ...	43
4	5 6.0	1 6.0	8 6.0	10 6.0	... ...	... ...	24
5	2 3.0	1 3.0	3 3.0	3 3.0	6 3.0	... ...	15
6+	2 1.6	0 1.6	0 1.6	2 1.6	2 1.6	4 2.0	10
Total	**66** **51.4**	**26** **51.4**	**26** **24.9**	**15** **10.6**	**8** **4.6**	**4** **2.0**	**145** **144.9**

*First number in each cell is the observed number; second is the expected number.

Prenatal Complications

Information on eight pregnancy events was obtained from the obstetrical records of 118 autistic children and 246 unaffected siblings. The events of interest were prenatal trauma requiring medical attention (falls, auto collisions, burns, or cuts); nausea with vomiting beyond the first trimester; light bleeding after the first trimester; heavy bleeding at any time; edema (+ + or more); toxemia; physician-attended maternal illness or febrile illness of at least two days' duration; and physician-prescribed drugs, excluding vitamin or iron supplements.

Excepting edema and toxemia, for all other events of interest, there was some elevation of risk for the autistic children. The excess in frequency ranged from a low of 10% for light bleeding after the first trimester to a high of 360% for maternal accidents and for heavy bleeding at any time during pregnancy. The difference in frequency of pregnancy complications between propositi and comparison subjects was significant ($P = .05$) for use of medication; differences between the two groups for other complications were not statistically significant. However, autistic children were significantly more likely than their siblings to have at least one of the listed complications ($P < .05$) (Table 3).

Table 3.—Prenatal Complications Recorded in Obstetrical Records

Complication	No. With Complication		Relative Risks*		95% Confidence Interval for Adjusted Relative Risk
	Propositi (N = 118)	Siblings (N = 246)	Unadjusted	Adjusted for Birth Order	
Maternal accident during pregnancy	5	3	3.3	3.3	0.3-35.7
Severe nausea after 12 weeks	24	41	1.3	1.3	0.9-2.0
Staining after 12 weeks	10	20	1.1	1.2	0.7-2.0
Heavy bleeding during pregnancy	5	3	3.6	5.2	0.8-30.4
Edema	21	45	1.0	1.1	0.8-1.5
Toxemia	4	10	0.8	0.9	0.5-1.5
Maternal illness of any kind during pregnancy	19	37	1.1	1.3	0.9-1.9
Medication of any kind during pregnancy	52	90	1.4	1.3	1.0-1.9
At least one of the above	78	152	1.2	1.5	1.1-2.0

*Maximum likelihood estimates of relative risk.

Labor and Delivery Complications

Eight complications of delivery were investigated. These were emergency cesarian sections, vaginal delivery aided by forceps, malposition of fetus, cord problems (which included both prolapse of cord and wrapping the cord around the child's neck), hemorrhage during delivery, unduly long labor (first stage lasting more than 12 hours), precipitous labor (labor lasting one hour or less), and maternal weight gain of less than 4.5 kg or more than 13.6 kg.

The number of propositi and siblings experiencing each complication, the unadjusted and adjusted relative risk estimates, and the 95% confidence limits around the estimates adjusted for birth order are given in Table 4. As in the case of pregnancy complications, the propositi sustained a higher frequency of labor and delivery difficulties. All eight events were more common for the propositi. The excess ranged from 10% for forceps-aided delivery to 560% for emergency cesarean sections. Emergency cesarean sections were always performed as a result of some prior complication during delivery and were not themselves complications. The reasons for emergency sections were fetal distress (two propositi, one sibling), placenta previa with hemorrhage (one propositus), failed labor (two propositi, one sibling), and cephalopelvic disproportion (five propositi, two siblings). Although the frequency of unfavorable events was low for both propositi and comparison subjects, there is a trend that suggests that autistic children experienced delivery complications more frequently than unaffected siblings. The difference between propositi and siblings was statistically significant only when all complications were grouped together.

Neonatal Complications

History of neonatal complications was obtained primarily from family interviews, as delivery records contained little information on the child's condition beyond birth weight and a comment on the child's general condition and appearance. Except for one instance in which a child was born with only one arm, there was no other medical notation of any malformations, although club feet, hip displacements, and other less severe malformations were reported by the mothers of 22 autistic children and 24 siblings. Information on birth weight and on the newborn's condition, based on strength of cry and color, was obtained from the medical records; data on delayed crying, the presence of malformations, the development of jaundice in the first few days of life, and on need for medical intervention in the first month of life were obtained from the family interview. Table 5 gives the data on neonatal complications.

Jaundice was the only neonatal complication that occurred with approximately equal frequency among propositi and siblings. For all other events, the autistic children bore an increased risk of complications. Medical intervention in the first month of life, including both minor procedures such as intubation and administration of oxygen and major procedures such as surgery, was significantly more common for the autistic children ($P = .05$).

Table 4.—Delivery Complications Recorded in Medical Records

Complication	No. With Complication		Relative Risk*		95% Confidence Interval for Adjusted Relative Risk
	Propositi (N = 118)	Siblings (N = 246)	Unadjusted	Adjusted For Birth Order	
Emergency section	10	4	5.6	5.3	0.3-108.6
Forceps delivery	71	146	1.1	1.1	0.9-1.4
Cord difficulties	21	35	1.5	1.6	0.9-2.5
Hemorrhage	8	6	2.9	3.6	0.5-25.9
Malposition	15	22	1.6	1.5	0.9-2.7
Prolonged 1st stage of labor (≥ 12 hr) •	18	21	2.1	1.3	0.8-2.1
Precipitous labor (≤ 1 hr)	6	7	1.8	2.4	0.6-9.4
Total weight gain < 4.5 or > 13.6 kg	26	50	1.1	1.2	0.9-1.7
At least one of the listed complications	101	196	1.5	1.4	1.0-1.8

*Maximum likelihood estimates of relative risk.

Table 5.—Neonatal Complications Based on Family and Medical Record Data*

Complication	No. With Complication		Relative Risk†		95% Confidence Interval for Adjusted Relative Risk
	Propositi	Siblings	Unadjusted	Adjusted for Birth Order	
Poor condition at birth	16	20	1.7	1.7	0.9-3.3
Weight < 2,270 g at birth	8	7	1.9	2.2	0.7-6.9
Slow to cry	6	4	3.5	3.3	0.4-28.3
Malformation	22	24	2.3	3.8	0.6-24.4
Jaundice	10	21	1.0	1.1	0.7-1.7
Need for medical intervention in 1st mo	24	37	1.6	1.6	1.0-2.6
At least one of the listed complications	51	69	2.1	2.0	1.3-3.0

*Data on subjects' condition at birth and on birth weight were obtained from medical records (118 propositi, 246 siblings). Information on all other complications was obtained from family interviews (145 propositi, 330 siblings).

†Maximum likelihood estimates of relative risk.

COMMENT

Several investigators have evaluated the prenatal and early infancy course of children who had a variety of behavioral disorders, including psychosis and mental retardation. Three of these investigations have concentrated specifically on children with autistic symptomatology.[2,7,14] In these studies, comparison groups have consisted both of siblings and of unrelated children, and of mentally retarded and normal nonautistic children. Results have indicated that in the prenatal phase, autistic children experienced an excess of complications only when compared with normal, unrelated comparison subjects; in the neonatal phase, autistic children had more untoward medical events than any of the three groups of comparison subjects. Specifically, maternal bleeding after the first trimester[15] and low birth weight[1,16] have been identified as variables associated with autism.

The results of the current study support previous findings and suggest that there is a consistent association of unfavorable events in pregnancy, delivery, and in the neonatal phase with autism. It is unlikely that these findings are subject to bias of ascertainment, since most of the analyses used data obtained from medical charts recorded long before autistic symptomatology was noted. While our findings are consistent with those of previous investigators, the interpretation of the results is difficult, as the highest risk ratios were observed for events that involved very small proportions of propositi and siblings, making it unlikely that these complications would account for any substantial number of cases of autism. The frequency of common complications was similar for propositi and unaffected siblings. Furthermore, complications that carried the highest risk of autism represented various kinds of pathologic processes with no apparent unifying feature. This lack of specificity may indicate that various types of physical damage may produce autistic symptomatology, but that no single complication or cluster of complication is responsible for the development of autism.

The data have indicated that an association exists between birth order and autism. If birth order were also related to the complications studied, then birth order could confound the association between pregnancy, delivery, and neonatal difficulties and autism. However, the risk ratios adjusted for the effect of birth order (Tables 3 through 5) do not differ from the unadjusted risk ratios for most of the complications. This finding implies that the first birth order carries an elevated and independent risk of autism that cannot be attributed to the possibly higher frequency of the investigated reproductive complications among first-born children. Nevertheless, one cannot exclude the possibility that other deleterious events or agents, not considered in this study, may be related both to autism and to birth orders. Should such a factor exist, it would be responsible for the observed association of autism and birth order.

The excess of first-born autistic children in small sibships has been noted by previous investigators[17-19] and is unlikely to be the result of bias due to incomplete sibships. In addition, a study by Wing[20] has, like this

investigation, reported both a marked excess of first-born autistic cases among small sibships and a moderate excess of autistic children in the last or penultimate birth orders of large sibships. Interpretation of this finding is complicated because of the bias introduced when one is dealing with incomplete sibships. This bias, which produces greater than expected numbers of cases in last birth orders, is strongest when the condition under study is ascertained at birth and when enrollment of subjects is at the time of diagnosis. The longer the interval between birth and symptom manifestation or between diagnosis and study enrollment, the less the effect of the bias. Although autism is not usually apparent at birth, it is generally diagnosed in early childhood. Thus, the effects of bias may be somewhat muted but cannot be discounted. However, there may be two other explanations for the observed birth order distribution. The first relates to parents' unwillingness to have more children after producing an autistic child. A decision to truncate family size after the birth of an autistic child may be more characteristic of parents who have several children than of parents who have no other children. A second interpretation is suggested by the work of Schoenbaum,[21] who evaluated the role of parity in congenital rubella syndrome. He has reported a bimodal birth order distribution very similar to the one found in our sample. Among cases of documented congenital rubella syndrome, he noted a large excess of first-born, a deficit of second- and third-born, and then again a modest excess of cases occupying birth orders 4 and beyond. The author suggests that the risk of prenatal rubella is greatest for the first-born because their primiparous mothers are not housebound and have work and recreational activities in the community. Children in late birth orders are again at risk because their mothers are potentially exposed to rubella via school-aged siblings. Because of the striking similarity in the birth order distribution among autistic children and victims of congenital rubella, the role of an infectious agent in the development of autism might be considered.

In a previous study,[11] we evaluated a number of infectious agents as possible factors in the etiology of autism. The data showed that, with the exception of prenatal rubella and prenatal influenza, the frequency of all other infectious agents under study was equally low for propositi and siblings. At most, only an estimated 5% of autism could be attributable to prenatal rubella or influenza infection. While these results do not eliminate the possibility of a specific infectious agent in the development of autism, they suggest that should such an agent exist it is not likely to be a common or easily recognized infection.

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References

1. Pasamanick B, Rogers M, Lilienfeld A: Pregnancy experience and the development of behavior disorder in children. *Am J Psychiatry* 112:613-618, 1956.

2. Taft L, Goldfarb W: Prenatal and perinatal factors in childhood schizophrenia. *Dev Med Child Neurol* 6:32-43, 1964.

3. Rutt CN, Offord DR: Prenatal and perinatal complications in childhood schizophrenia and their sibships. *J Nerv Ment Dis* 152:324-331, 1971.

4. Ritvo ER, Ornitz EM, Walker RD, et al: Correlation of psychiatric diagnoses and EEG findings: A double-blind study of 184 hospitalized children. *Am J Psychiatry* 126:988-996, 1970.

5. De Myer MK: Research in infantile autism: A strategy and its results. *Biol Psychiatry* 10:433-450, 1975.

6. Houser SL, DeLong R, Rosman NP: Pneumographic findings in the infantile autism syndrome. *Brain* 98:667-688, 1975.

7. Kolvin I, Ounstead C, Roth M: Cerebral dysfunction and childhood psychosis. *Br J Psychiatry* 118:407-414, 1971.

8. Deykin EY, MacMahon B: The incidence of seizures among children with autistic symptoms. *Am J Psychiatry* 136:1310-1312, 1979.

9. Rutter M: Behavioral and cognitive characteristics of a series of psychotic children, in Wing JK (ed): *Childhood Autism: Clinical, Educational and Social Aspects.* London, Pergamon Press, 1966.

10. De Myer MK, Barton S, Alpern G, et al: The measured intelligence of autistic children. *J Autism Child Schizophr* 4:42-60, 1974.

11. Deykin EY, MacMahon B: Viral exposure and autism. *Am J Epidemiol* 109:628-638, 1979.

12. Rothman K: Computer analysis for case-control studies with individual matching. *Int J Biomed Comput* 5:241-247, 1974.

13. Greenwood M, Yule GU: On the determination of size of family and of the distribution of characters in order of birth from samples taken through members of the sibships. *J Statist Soc* 77:179-197, 1914.

14. Knobloch H, Pasamanick B: Some etiologic and prognostic factors in early infantile autism and psychosis. *Pediatrics* 55:182-191, 1975.

15. Torrey EF, Hersh SP, McCabe KD: Early childhood psychosis and bleeding during pregnancy. *J Autism Child Schizophr* 3:287-297, 1975.

16. Lane EA, Albee GW: Comparative birth weights of schizophrenics and their siblings. *J Psychol* 64:227-231, 1966.

17. Kanner L: To what extent is early infantile autism determined by constitutional inadequacies. *Proc Assoc Res Nerv Ment Dis* 33:378-385, 1954.

18. Rutter M, Lockyer L: A five to fifteen year follow-up of infantile psychosis. *Br J Psychiatry* 113:1183-1199, 1967.

19. Creak EH, Ini S: Families of psychotic children. *J Child Psychol Psychiatry* 1:156-175, 1960.

20. Wing JK: Diagnosis, epidemiology, aetiology, in Wing JK (ed): *Childhood Autism: Clinical, Educational and Social Aspects.* London, Pergamon Press, 1966.

21. Schoenbaum S, Biano S, Mack T: Epidemiology of congenital rubella syndrome: The role of maternal parity. *JAMA* 233:151-155, 1975.

Fluoride Supplements for Children

A Survey of Physicians' Prescription Practices

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• **We present the results of a survey to determine how physicians prescribe fluoride supplements for their child patients. A questionnaire was mailed to a representative nationwide sample of 2,604 physicians who treat children. The response rate of completed returns was 49.4%. Results showed that while most respondents prescribed fluoride appropriately, there was some inappropriate prescribing for children receiving fluoridated water. Some physicians also neglected to prescribe for children who were not receiving fluoridated water. Previous differences in recommended schedules of administration between the American Academy of Pediatrics and the American Dental Association may have led to some of these problems. However, these two organizations have now standardized their recommendations.**

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Although the effectiveness of fluoride in the prevention of dental caries has been well researched, documented, and accepted,[1-6] there is little information regarding the nature and extent of the prescription of fluoride supplements by physicians who care for pediatric patients. Approximately 50% of the nation's children live in areas of the United States with inadequate amounts of fluoride in the water supply.[7] In the absence of school-based preventive programs, these children can receive adequate amounts of fluoride only through prescribed fluoride supplements.

We present the results of a nationwide mail survey among physicians who treat children. The aim of the survey was to determine the physicians' patterns of prescribing fluoride supplements for their child patients. Subsequently, an educational project aimed at improving the identified problems has begun.

This study focused on physicians who treat children, rather than focusing on dentists, because only 13% of American children have visited a dentist by age 5,[8] when all of the primary teeth and most permanent teeth are completely calcified. While it is recommended that all preschool-aged children visit a dentist, until their utilization of dental services improves physicians will carry the primary responsibility for ensuring correct fluoride supplementation among children.

METHODS

Sample Design

The sampling frame, supplied by Ross Laboratories, Columbus, Ohio,[8] was a computerized list of all physicians in the United States identified as having some pediatric practice. Ross Laboratories is continually updating this list, which is their basic source of commercial contact with physicians, and so it was considered to be at least as current as existing physician directories. It had the added advantage of identifying the physicians as pediatricians (both MD and DO) or family practitioners (again, both MD and DO).

The Fluoridation Census of 1975,[7] published by the then Department of Health, Education, and Welfare, was used to identify whether the practice location of physicians was in a fluoridated or nonfluoridated area. A differentiation was made between (*a*) physicians practicing in large fluoridated areas (those with a population over 500,000), (*b*) physicians practicing in less populated fluoridated areas, and (*c*) physicians practicing in nonfluoridated areas. "Fluoridated" was defined as a concentration of 0.7 ppm or more of fluoride in the municipal water supply.

The physician list was stratified by physician type and by fluoridation status of the practitioner's locality. Variable sampling fractions were employed within each stratum to give the desired number of physicians in the sample. Table 1 gives the numbers of physicians selected in the sample and the number of completed questionnaires received.•

Conduct of the Study

The questionnaire was designed to solicit information from the physicians on (*a*) their attitudes toward fluoride supplementation and their perception of their respon-

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Table 1.—Physicians Selected and Responding to Questionnaire, by Practice Type and Location

Practice	Location of Practice: Large Cities With Fluoridation	Less Populated Fluoridated Areas	Nonfluoridated Areas	Total
Physicians Selected				
Pediatricians	200	615	781	**1,596**
Family practitioners	128	390	490	**1,008**
Total	**328**	**1005**	**1,271**	**2,604**
Physicians Responding				
Pediatricians	103 (51.5%)	350 (56.9%)	510 (65.3%)	**963** (60.3%)
Family practitioners	20 (15.6%)	142 (36.4%)	161 (32.9%)	**323** (32.0%)
Total	**123** (37.5%)	**492** (49.0%)	**671** (52.8%)	**1,286** (49.4%)

Table 2.—Physicians Prescribing Dietary Supplement of Fluoride

Practice	Location of Practice: Large Cities With Fluoridation	Less Populated Fluoridated Areas	Nonfluoridated Areas	Total
Pediatricians	50 (48.5%)	278 (79.4%)	453 (88.8%)	**781** (81.1%)
Family practitioners	7 (35.0%)	70 (49.3%)	126 (78.3%)	**203** (62.8%)
Total	**57** (46.3%)	**348** (70.7%)	**579** (86.3%)	**984** (76.5%)

Table 3.—Recommended Dosage Levels of Supplemental Fluoride

Age, yr	Fluoride Concentration, ppm: 0.0-0.3 (mg/Day)	0.3-0.7 (mg/Day)	0.7+ (mg/Day)
0-2	0.25	0.0	0.0
2-3	0.50	0.25	0.0
3-13	1.00	0.50	0.0

*By age and concentration of fluoride in drinking water, Levels recommended by the American Dental Association and the American Academy of Pediatrics. The American Academy of Pediatrics recommends 16, rather than 13, as the termination age.

sibility in providing the necessary prescriptions, (*b*) their knowledge of the efficacy of fluoride and the need for fluoride supplementation among their patients, and (*c*) their actual practice in prescribing fluoride supplements, including the dosage and ages at which fluoride was prescribed.

The questionnaire, which took about seven minutes to complete, was pretested in a volunteer group of physicians participating in a continuing education program at the University of Michigan Medical School.

The initial mailing of the questionnaires in late 1978 was accompanied by a cover letter individually addressed to each physician. A second mailing after three weeks was made to all physicians who did not return the questionnaire the first time. Finally, a 25% sample of nonrespondents was contacted by telephone in order to request their cooperation in the study. As a result of these efforts, 1,771 of the 2,986 sampled physicians (2,604 MDs and 382 DOs) returned their questionnaires. Three hundred twenty-one of these questionnaires were returned unanswered, 158 by practicing physicians who did not treat pediatric patients. The next most common reason for not answering the questionnaire was that the physician was in specialist pediatric practice. Other reasons for noncompletion were that the sample physicians were interns, administrators, teachers, or researchers. The total number of completed questionnaires returned was therefore 1,450.

Only 164 of the 1,450 completed questionnaires came from osteopaths, and their responses were similar to those given by the medical physician respondents. Because the number of osteopaths in some cells of the analysis was very small, osteopaths were omitted from the results given in this paper. Results given, therefore, are for pediatricians holding MD degrees and family practitioners only. There were 1,286 completed questionnaires received from the 2,604 medical physicians in the sample, a response rate of 49.4%.

RESULTS

Overall recognition of the importance of fluoride in the prevention of dental caries was high; 91.9% of pediatricians and 86.5% of family practitioners responded that usage of fluoride was either important or very important in the prevention of dental caries. More than one third (37.2%) of the physicians correctly identified that ingestion of recommended amounts of fluoride can be expected to reduce the incidence of dental caries in children by 50% to 75%. A further 10.8% of physicians overestimated the potential effectiveness of fluoride, and only 5.7% underestimated the reduction in caries incidence.

More than 94% of the physicians, regardless of the fluoride status of water in their practice location, reported that helping to prevent dental disease by appropriate prescription of fluoride was part of their responsibility to their patients. Yet, when asked whether they prescribed fluoride supplements, 18.9% of the pediatricians and 37.2% of the family practitioners responded that they did not (Table 2). Some of these respondents, of course, were practicing in areas where almost all of their patients were receiving municipally fluoridated water, in which case prescription of supplemental dietary fluorides would be inappropriate. But even among those physicians practicing in nonfluoridated areas, 11.2% of pediatricians and 21.7% of family practitioners reported that they did not prescribe fluoride supplements at all. Table 2 gives the reported prescribing patterns by physician type and location of practice.

At the other end of the scale, 46.3% of physicians in large fluoridated cities and 70.7% of those in smaller fluoridated areas prescribe fluoride supplements. On the face of it, these prescriptions seem inappropriate. However, some patients of these physicians, especially those attending the physicians in smaller fluoridated communities, may have come from adjoining areas without fluoridated water.

Other patients may have been breast-fed infants, who require special consideration (and were the subject of specific questions to be considered later in this report).

While prescribing pediatricians and family practitioners both generally commenced their prescriptions for infants around the recommended[9,10] 3 to 4 months of age, 58.1% of pediatricians and 52.7% of family practitioners prescribed 0.5 mg or more (rather than the now recommended 0.25 mg[9,10]) as the initial daily dose of fluoride supplement. (It should be noted that this survey was conducted before the American Academy of Pediatrics revised its recommended initial dosages down from 0.5 to 0.25 mg/day,[10] so these results are not unexpected.) In addition, 13.8% of pediatricians and 31.9% of family practitioners did not answer this question. Only 59.9% of prescribing pediatricians and 44.8% of family practitioners stated that they revised this initial dosage with increasing patient age. In both groups most physicians said that they did so at about 2 years of age. Among those physicians who revised their dosages, 60.0% of pediatricians and 70.3% of family practitioners both usually discontinued prescribing fluoride supplements at a mean age of approximately 9 years. (Table 3 gives the recommended regimen[9,10] for prescription of fluoride supplements.)

Physicians who do prescribe fluoride supplements were asked for their prescribing practices for infants up to 1 year of age, according to whether the child was breast-fed or bottle-fed and whether the municipal water supply was fluoridated or not. Responses are given in Table 4. Though a substantial majority of these physicians correctly prescribed fluoride where drinking water was not fluoridated, it can be seen that 10% to 13% of pediatricians and 17% to 20% of family practitioners reported that they prescribed fluoride supplement for bottle-fed infants who drink fluoridated water. Such prescriptions are inappropriate, as children receiving an excess of fluoride can later exhibit some mild fluorosis in permanent teeth.[11]

Table 4.—Physicians Prescribing Fluoride for Breast-fed and Bottle-fed Babies

Patient Category; Practice	Patient Age: 0-6 mo Physicians Prescribing No.	0-6 mo Physicians Prescribing %	6 mo–1 yr Physicians Prescribing No.	6 mo–1 yr Physicians Prescribing %
Breast-fed babies; mothers drink fluoridated water				
Pediatrician	343	43.9	421	53.9
Family practitioner	67	33.0	82	40.4
Breast-fed babies; mothers drink nonfluoridated water				
Pediatrican	618	79.1	684	87.6
Family practitioner	159	78.3	162	79.8
Bottle-fed babies, drink fluoridated water				
Pediatrician	84	10.8	98	12.5
Family practitioner	35	17.2	39	19.2
Bottle-fed babies, drink nonfluoridated water				
Pediatrician	617	79.0	703	90.0
Family practitioner	167	82.3	170	83.7

COMMENT

The combined response rate of 49.4% (60.3% of the pediatricians and 32.0% of the family practitioners) is reasonable for a mail survey of professionals, but it is still lower than desirable. Results of the survey must be interpreted in light of this response rate. As it is probable that the more conscientious and knowledgeable physicians responded, the deficiencies in prescribing behavior identified may in fact be worse than the results of this survey indicate. With respect to the validity of the sampling frame, the fact that only 158 of 1,771 returned questionnaires (8.9%) were from practicing physicians who did not treat pediatric patients suggested that the sampling frame used was adequate. Both responding physician groups were aware of the benefits of the appropriate supplementation with fluoride and reported acceptance of their responsibility in helping to prevent tooth decay. But unacceptably high proportions of pediatricians and even higher proportions of family practitioners provided no fluoride prescriptions for their patients when a need for them clearly existed (Table 2).

Part of the reason for this gap between knowledge and behavior might be found in the comments given by some of the physician respondents. These comments suggested that some parents were concerned about possible adverse effects of the supplements and that the physicians lacked sufficiently detailed knowledge to answer these concerns. Other physicians reported that some noncompliant behavior had led them to cease prescribing fluoride supplements for all patients. It would thus seem that while physicians are aware of the general effect of fluoride, many require more specific knowledge to help them prescribe it more appropriately.

The need for more information on the use of fluoride supplements was in fact identified by the physicians themselves. Two thirds reported a lack of readily accessible current information concerning the effect of fluoride supplements. They stated that they had learned little about fluoride during their professional education, including the pediatric internship or residencies where applicable, and that they had learned more from continuing education programs, professional journals, and dentists.

A major area of concern identified in the study was that most respondents who did prescribe fluoride supplements prescribed too high a dosage

at an early age and then ceased prescribing too early. Supplementation for fluoride should continue until eruption of all teeth (except the third molars) has been completed, that is, usually until age 13.[9]

Probably the major reason for the prescription of higher-than-necessary doses at an early age was the previous differences between the dosage schedules recommended by the American Academy of Pediatrics (AAP) and the Council on Dental Therapeutics of the American Dental Association (ADA). The AAP has recently revised its recommendations to bring them into line with those of the ADA[10]; what is now the jointly recommended schedule is given in Table 3. The one minor difference in the schedules recommended by the two bodies is in termination age.

Varying degrees of mild enamel fluorosis have been reported[12,13] at the higher dosages previously recommended by the AAP,[14] although others have not found such to be the case.[2] The ADA acknowledges the need for additional research on the most suitable dosage schedule for fluoride supplementation,[15] although the current empirically derived schedule is conservative and has evolved cautiously with the experience of many years. However, it can be stated that there is little justification for a child drinking fluoridated water to receive supplemental fluoride.

Breast-fed infants in a non-fluoridated area should receive fluoride supplementation from birth,[15,16] as this regimen will give additional protection to the calcifying primary teeth with little risk of fluorosis in the permanent dentition. A modified approach is required where water is optimally fluoridated. Although human milk contains insignificant amounts of fluoride,[17] the attending physician needs to determine whether the child is being totally breast-fed or whether the diet is being supplemented by additional food and water. If the latter, physicians in fluoridated areas are advised not to prescribe fluoride supplements in order to avoid the risk of mild enamel fluorosis. If the physician is confident that the child is being totally breast-fed, the AAP-ADA schedule in Table 3 can be followed until weaning,[16] regardless of fluoridation status.

The educational follow-up to this study, designed to provide comprehensive information on fluoride to all practicing physicians who treat children in the United States, seeks to provide all of these physicians with audiotapes, films, and exhibits on recommended fluoride supplementation. All teaching institutions will also receive a portfolio on the subject. It is hoped that this project will serve to remedy the deficiencies in prescribing fluoride identified in this project.

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References

1. McClure FJ: *Water Fluoridation: The Search and the Victory.* Bethesda, Md, National Institutes of Health, 1970.

2. Margolis FJ, Reames HR, Freshman E, et al: Fluoride: Ten-year prospective study of deciduous and permanent dentition. *Am J Dis Child* 130:794-800, 1975.

3. Burt BA (ed): *The Relative Efficiency of Methods of Caries Prevention in Dental Public Health: Proceedings of a Workshop.* Ann Arbor, Mich, University of Michigan Press, 1978.

4. World Health Organization: Fluoridation and general health. *WHO Chron* 23:505-512, 1969.

5. World Health Organization: Twenty-eighth World Assembly-2. *WHO Chron* 29:289-299, 1975.

6. World Health Organization: Decisions of the health assembly. *WHO Chron* 32:270, 1978.

7. US Public Health Service, Center for Disease Control: *Fluoridation Census 1975.* Atlanta, Government Printing Office, 1977.

8. US Public Health Service, National Center for Health Statistics. *Dental Visits: Volume and Interval Since Last Visit. United States—1969.* US Dept of Health, Education, and Welfare, Publication No. (HSM) 72-1066, 1972.

9. American Dental Association: *Accepted Dental Therapeutics,* ed 37. Chicago, ADA, 1977.

10. American Academy of Pediatrics Committee on Nutrition: Fluoride supplementation: Revised dosage schedule. *Pediatrics* 63:150-152, 1979.

11. Corpron RE, Burt BA: Fluorosis from supplementation with fluoride tablets: A case report. *Mich Dent Assoc J* 60:6105-6108, 1978.

12. Aasenden R, Peebles TC: Effects of fluoride supplementation from birth on human deciduous and permanent teeth. *Arch Oral Biol* 19:321-326, 1974.

13. Hennon DK, Stookey GK, Beiswanger BB: Fluoride-vitamin supplements: Effects on dental caries and fluorosis when used in areas with suboptimum fluoride in the water supply. *Am Dent Assoc J* 95:965-971, 1977.

14. American Academy of Pediatrics Committee on Nutrition: Fluoride as a nutrient. *Pediatrics* 49:456-459, 1972.

15. Driscoll WS, Horowitz HS: A discussion of optimal dosage for dietary fluoride supplementation. *Am Dent Assoc J* 96:1050-1053, 1978.

16. Driscoll WD, Horowitz HS: Dosage recommendations for dietary fluoride supplements. *Am J Dis Child* 133:683-684, 1979.

17. Hodge HC, Smith FA, Gedalia I: Excretion of fluorides, in *Fluorides and Human Health.* Geneva, World Health Organization, 1970, p 141.

CNS Manifestations of the Hemolytic-Uremic Syndrome

Relationship to Metabolic Alterations and Prognosis

James F. Bale, Jr, MD; Craig Brasher, MD; Richard L. Siegler, MD

• To define the CNS manifestations of the hemolytic-uremic syndrome (HUS), the records of 61 consecutive episodes of HUS in 60 patients were reviewed. Major CNS signs (seizures and/or coma) occurred in 30 of the 61 episodes. Twenty-four children had seizures. Analysis of blood pressure and metabolic parameters on admission to the hospital did not predict which child would exhibit CNS signs. However, during the subsequent course of the illness, children with CNS dysfunction had lower minimum serum sodium concentrations and more severe azotemia and were more likely to require dialysis than children without CNS signs. Of the 61 episodes, there were three deaths, and three children suffered major CNS sequelae. Coma at the time of admission and elevated CSF protein levels were features associated with poor outcome.

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The hemolytic-uremic syndrome (HUS) is the most common cause of acute renal failure in infants and young children. The principal features include (1) antecedent gastroenteritis or upper respiratory tract infection, (2) acute onset of microangiopathic hemolytic anemia and thrombocytopenia, (3) acute renal failure, and (4) frequent involvement of the CNS.[1-5]

To define factors important in the pathogenesis of the CNS abnormalities and to identify features that predicted death or CNS sequelae, a detailed retrospective study of the clinical and laboratory features of 61 episodes of HUS in 60 children were performed.

PATIENTS AND METHODS

Patient Population

The records of 61 consecutive episodes of HUS in 60 patients (one child had two distinct episodes) admitted to the Primary Children's and University of Utah Medical Centers, Salt Lake City, between the years of 1972 and 1978 were reviewed. The cases represented a referral population from the states of Utah, Wyoming, and Idaho. The children ranged in age from 3 months to 13 years (average age, 3.3 years). No epidemics of HUS were identified during the seven-year study interval.

Clinical Features

The features of the prodromal illness included diarrhea and vomiting in over 90% of the children. Fever, pallor, symptoms of upper respiratory tract infection, and oliguria occurred less commonly. The subsequent clinical course included oliguria or anuria in 64% and hypertension in 51% of the cases. Thirty-three children (54%) required dialysis (BUN level, >150 mg/dL) and 39 (65%) of the children received one or more blood transfusions.

Central nervous system dysfunction was seen in 30 of the 61 episodes (48%) (Table 1). Twenty-four children experienced seizures, and alterations of consciousness without seizures occurred in an additional six children. The seizures were generalized tonoclonic in 20 children and focal in four. In most children the seizures occurred early in the illness (average, 6.5 days after the onset of the prodrome) and were often seen within the first 72 hours after admission. In nine children, a seizure was the clinical manifestation that led to the child's hospi-

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Table 1.—Acute Neurologic Complications in Hemolytic-Uremic Syndrome (61 Episodes)

Complications	No.	%
Seizures	24	40
Generalized	20	33
Focal	4	7
Altered consciousness without seizures	6	10
Decerebrate posturing	2	3
Hemiparesis (transient)	1	2

talization. When seizures did occur, they were usually isolated events, and in only nine children did multiple seizures (more than two) occur.

Although alterations of consciousness were common and included a spectrum from lethargy to coma, profound coma at the time of admission was unusual and occurred in only five of the 61 episodes. Two children demonstrated decerebrate posturing and one child experienced a transient hemiparesis in association with focal seizures.

Laboratory Features

Values from the following laboratory studies were obtained for all children on admission to the hospital: serum sodium, glucose, calcium, hematocrit, BUN, and creatinine. Admission laboratory values were defined as the initial laboratory assessment obtained either at the referral hospital or at the Primary Children's and University of Utah Medical Centers for those admitted directly. Mean values and ranges for these laboratory parameters are presented in Table 2. For each child the lowest serum sodium, lowest calcium, lowest hematocrit, highest BUN, and highest creatinine value that occurred during hospitalization were also compiled (Table 3). All children exhibited proteinuria and hematuria, and in 72% a BUN level greater than 100 mg/dL was observed. The hematocrit was less than 25% and the platelet count was less than 100,000/cu mm in 97% and 74% of the children, respectively.

In children who incurred CNS symptoms during the course of their HUS illness, values for serum sodium, glucose, calcium, hematocrit, BUN, creatinine, blood pressure, and temperature were obtained at the time of the child's acute CNS dysfunction (Table 4).

Nineteen of the 30 children with CNS symptoms underwent lumbar puncture. The CSF glucose concentrations were normal and pleocytosis was absent, but two of the 19 children had an elevated CSF protein concentration (>50 mg/dL). An EEG was obtained in 11 of the 30 children who exhibited CNS symptoms. The EEG was diffusely slow in nine, normal in one, and isoelectric in one child who died within 48 hours after the onset of his illness. Three children exhibited epileptiform spike and/or sharp wave discharges.

Table 2.—Admission Laboratory Values*

Laboratory Values	CNS Signs and Symptoms: Present (N = 30) Mean ± SD	CNS Signs and Symptoms: Absent (N = 31) Mean ± SD	P†
Serum sodium, mEq/L	130 ± 8 (113-145)	135 ± 9 (107-146)	< .05
Blood glucose, mg/dL	133 ± 74 (49-386)	108 ± 28 (60-127)	NS
Serum calcium, mg/dL	8.0 ± 1 (6.0-10.3)	8.3 ± .9 (7-9.3)	NS
Hematocrit, %	30.5 ± 8 (19-45)	26.4 ± 9 (16-48)	NS
BUN, mg/dL	99.7 ± 63 (12-246)	75.8 ± 53 (9-203)	NS
Serum creatinine, mg/dL	6.6 ± 4.9 (0.5-17.0)	3.3 ± 3.1 (0.5-12.7)	< .01

*Numbers in parentheses indicate range.
†Student's *t* test.

Table 3.—Extremes of Laboratory Values*

Laboratory Values	CNS Signs and Symptoms: Present (N = 30) Mean ± SD	CNS Signs and Symptoms: Absent (N = 31) Mean ± SD	P†
Lowest serum sodium, mEq/L	124 ± 6 (113-140)	132 ± 8 (106-142)	< .001
Lowest serum calcium, mg/dL	7.5 ± 1 (5.3-8.9)	8.1 ± .8 (7-9.3)	NS
Lowest hematocrit, %	17.5 ± 3.5 (13-30)	18.6 ± 4.4 (12-35)	NS
Maximum BUN, mg/dL	158 ± 52 (27-295)	104 ± 65 (14-257)	< .01
Maximum serum creatinine, mg/dL	8.9 ± 4.8 (0.9-19.8)	4.9 ± 4.5 (0.5-15.6)	< .01

*Numbers in parentheses indicate range.
†Student's *t* test.

Comparison of laboratory parameters between subpopulations of children who did and did not exhibit CNS symptoms gave the following results. Admission laboratory studies (Table 2) revealed no significant differences ($P > .05$, Student's t test) in serum glucose, calcium, BUN, or hematocrit values. Slight differences in sodium ($P < .05$, Student's t test) and creatinine ($P < .01$, Student's t test) concentrations were seen, however. In the subsequent hospital course (Table 3), the children with CNS dysfunction tended to have lower minimum serum sodium ($P < .001$, Student's t test), higher BUN ($P < .01$, Student's t test), and higher serum creatinine ($P < .01$, Student's t test) concentrations than children who were without CNS complications. The higher BUN and serum creatinine values in the children with CNS complications resulted in more frequent peritoneal dialysis. The criterion for dialysis was a BUN concentration greater than 150 mg/dL. Twenty-four of the 30 children with CNS symptoms required dialysis. In contrast, only nine of 31 children who were free of CNS disease required dialysis. Peak BUN levels among children who underwent dialysis did not differ for either group (mean, 175 mg/dL).

MORBIDITY AND MORTALITY

Of the 60 children in this series, 57 (95%) are alive at one to seven years following their illness. Two deaths (3%) occurred during the acute phase of HUS, and one child died subsequently from a complication of chronic renal failure. Long-term major renal sequelae among survivors include hypertension in three (5%) and chronic renal failure in one child. Three children (5%) have suffered major neurologic sequelae. One child has generalized seizures, one exhibits psychomotor retardation, and one child is

Table 4.—Metabolic Alterations During Neurologic Dysfunction

Patient/Age	CNS Signs and Symptoms	Laboratory Values*				
		Serum Sodium, mEq/L	Serum Calcium, mg/dL	BUN, mg/dL	Blood Glucose, mg/dL	Hematocrit, %
1/12 yr	Focal seizure	135	8.7	174	168	18
2/15 mo	Generalized seizure	127	ND	74	109	43
3/6 mo	Focal seizure	122	8.3	102	91	17
4/3½ yr	Generalized seizure	114	ND	98	197	29
5/2 yr	Generalized seizure	128	7.9	97	130	33
6/3½ yr	Coma, generalized seizure	120	6.6	51	49	23
7/3½ yr	Generalized seizure	143	7.1	88	96	19
8/3 yr	Generalized seizure	128	ND	66	ND	25
9/14 mo	Focal seizure	125	7.7	85	167	29
10/2½ yr	Generalized seizure	129	6.2	161	100	34
11/20 mo	Coma, generalized seizure	133	7.1	80	280	35
12/2½ yr	Generalized seizure	137	ND	116	165	26
13/7½ yr	Lethargy	137	6.4	228	98	20
14/16 mo	Coma	142	ND	106	ND	27
15/7 mo	Generalized seizure	145	8.1	150	386	20
16/5 yr	Generalized seizure	118	7.2	92	110	23
17/3½ yr	Hallucinations	132	8.9	23	105	26
18/16 mo	Generalized seizure	128	7.8	51	273	34
19/6 yr	Coma, generalized seizure	134	ND	140	146	18
20/3 yr	Generalized seizure	117	9.3	72	148	22
21/13 mo	Generalized seizure	132	8.3	129	115	30
22/13 mo	Coma	123	ND	43	119	33
23/14 mo	Status seizure	116	8.4	76	130	38
24/1 yr	Generalized seizure	127	9.0	160	67	31
25/18 mo	Generalized seizure	132	6.6	179	ND	21
26/2 yr	Lethargy	124	ND	175	ND	16
27/15 mo	Generalized seizure	121	8.1	62	61	ND
28/13 yr	Combative	126	8.8	274	175	ND
29/2 yr	Generalized seizure	144	8.3	62	198	ND
30/7 yr	Focal seizure	140	8.2	80	109	23

*ND, not determined.

retarded and cortically blind. Major renal and neurologic sequelae have occurred concurrently in only one child. All of the children who died of acute HUS or sustained permanent damage to the nervous system were among the children who experienced CNS dysfunction during the acute phase of HUS.

COMMENT

Several authors, in particular Gianantonio and associates, have emphasized the importance of neurologic signs and symptoms in HUS.[2,5,8] Neurologic abnormalities can be minor, such as irritability, lethargy, and ataxia, but are often severe and include seizures, coma, and hemiparesis. In the series of 678 patients described by Gianantonio et al, 41% experienced major CNS dysfunction (stupor, coma, convulsions, and/or hemiparesis).[5] Other authors have encountered serious neurologic complications less frequently.[1,6]

In this study, 30 of the 60 children (50%) exhibited major CNS dysfunction during their illness. Seizures occurred in 24 (40%), and stupor or coma without seizure activity was seen in an additional six children (10%). Decerebrate posturing and transient hemiparesis were considerably less frequent. When seizures did occur, they were usually brief and were rarely recurrent. They often occurred early in the illness, and in nine children (15%) a seizure was the clinical feature that led to the child's hospitalization. In the majority of childen acute anticonvulsant therapy with phenytoin sodium, phenobarbital, and/or diazepam was utilized, but in only two children was anticonvulsant therapy continued at the time of discharge from the hospital.

Several mechanisms have been proposed to explain the CNS symptoms that accompany HUS. It has been suspected that the neurologic features could be the result of vascular occlusive lesions similar to those which are present in the kidney. However, such CNS lesions have only rarely been identified. In one of the few detailed neuropathological investigations of children who died during the acute stages of HUS, Rooney and co-workers[8] were unable to identify a distinctive neuropathologic process which could be considered typical for HUS.[10] The changes they noted were nonspecific and consisted primarily of edema and hypoxic damage. In contrast, Upadhyaya and co-workers suggested that microthrombi may be found in numerous organs, including the brain. They identified cerebral microthrombi in two of three autopsied cases.[11]

In our series, one of the two deaths from acute HUS (case 22) came to

autopsy. Although microthrombi were identified in the kidneys, microthrombi were not seen in the CNS. Edema and anoxic damage were the only neuropathologic abnormalities noted.

The numerous metabolic alterations that occur during HUS have also been implicated in the pathogenesis of the CNS dysfunction. Gianantonio and others have indicated that in some cases hypotonic overhydration, hypoglycemia, hypocalcemia, hyponatremia, or changes in serum osmolality have been associated with the CNS symptoms.[1,5,7] Hypertension has been cited as an additional factor.[9]

In this series, analysis of blood pressure and admission laboratory parameters (Table 2) did not predict which child would exhibit CNS dysfunction during the subsequent course of HUS. However, among the 30 children in whom CNS symptoms did develop, potential immediate metabolic causes could be identified in more than half (Table 4). Hyponatremia (Na^+ <130 mEq/L) and/or vigorous hydration with hypotonic fluids was temporally associated with seizures or altered consciousness in 17 children and an additional ten children had hypocalcemia (Ca^{++} <8.0 mg/dL). One child (case 6) was febrile (temperature >38.6 °C). Two additional children (cases 7 and 30) experienced late onset seizures (days 14 and 15 of illness) following peritoneal dialysis. No child had hypoglycemia (glucose <45 mg/dL) or hypertensive encephalopathy at the time of acute CNS dysfunction.

Our patients with CNS symptoms had lower minimum serum sodium concentrations, higher peak BUN and serum creatinine concentrations, and were more likely to require dialysis during the subsequent course of HUS than were children without CNS signs or symptoms (Table 3). This suggests that a combination of metabolic alterations may have been operative in the pathogenesis of the CNS dysfunction in our patients. This is further supported by the observation that children with seizures and/or coma were more likely to have a low serum sodium concentration (<130 mEq/L) and/or a high BUN level (>100 mg/dL) during their illness than were children without CNS signs ($P < .001$; χ^2).

Long-term morbidity occurred in six of the 60 children in this series (10%). Three suffered major damage to the nervous system. As suggested by both Rooney and associates[8] and Gianantonio and associates,[5] the occurrence of CNS dysfunction was associated with increased morbidity and mortality. All of the children who died of acute HUS (2/60) or incurred major CNS sequelae (three of 57 survivors) were among children who experienced CNS dysfunction during the acute phase of HUS. Coma at the time of admission was the most important predictor of outcome, and of the five children who were comatose on admission, two died and two were left with severe CNS sequelae. Although seizures were common during the acute stage of HUS, they did not by themselves predict death or CNS sequelae.

The level of CSF protein was an additional feature that may assist in predicting prognosis. Of the two children with elevated CSF protein levels (>50 mg/dL), one died of acute HUS and the other was rendered cortically blind. None of the other 17 children with normal CSF protein levels experienced death or poor outcome ($P < .001$; χ^2).

Patricia Gay, PhD, provided statistical assistance. Margaret Grunnet, MD, assisted with the neuropathologic examinations.

References

1. Lieberman E: Hemolytic uremic syndrome. *J Pediatr* 80:1-16, 1972.

2. Gianantonio CA, Vitacco M, Mendilaharzu F, et al: The hemolytic uremic syndrome. *J Pediatr* 64:478-491, 1964.

3. Lieberman E, Heuser E, Donnell GN, et al: Hemolytic-uremic syndrome. *N Engl J Med* 275:227-236, 1966.

4. Piel CF, Phibbs RH: The hemolytic-uremic syndrome. *Pediatr Clin North Am* 13:295-314, 1966.

5. Gianantonio CA, Vitacco M, Mendilaharzu F, et al: The hemolytic-uremic syndrome. *Nephron* 11:174-192, 1973.

6. Tune BM, Leavitt TJ, Gribble TJ: The hemolytic uremic syndrome in California: A review of 28 non-heparinized cases with long-term follow-up. *J Pediatr* 82:304-310, 1973.

7. Sorrenti LY, Lewy PF: The hemolytic-uremic syndrome. *Am J Dis Child* 132:59-62, 1978.

8. Rooney JR, Anderson RM, Hopkins IJ: Clinical and pathological aspects of the central nervous system involvement in the hemolytic uremic syndrome. *Aust Paediatr J* 7:28-33, 1971.

9. Kaplan BS, Thomson PD, Chadarevian JP: The hemolytic uremic syndrome. *Pediatr Clin North Am* 23:761-777, 1976.

10. Meadows R: Central nervous system involvement in the hemolytic uremic syndrome. *Dev Med Child Neurol* 13:812-814, 1971.

11. Upadhyaya K, Barwick K, Fishaut M, et al: The importance of nonrenal involvement in hemolytic-uremic syndrome. *Pediatrics* 1:115-120, 1980.

Inappropriate Secretion of Antidiuretic Hormone After Open Heart Surgery

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• **After open heart surgery for the closure of an atrial septal defect, acute brain syndrome developed in a 5-year-old girl, this being documented by laboratory evidence of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Irritability and total disorientation were the first symptoms observed. She completely recovered after being treated with hypertonic saline solution and fluid restriction. The potentially serious outcome of the SIADH warrants early recognition and appropriate measures in children who suffer acute brain syndrome after open heart surgery.**

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Since the original description by Schwartz et al in 1957,[1] the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been recognized in postoperative patients and in association with many disorders, including CNS disease, malignant neoplasms, and pulmonary diseases.[2] However, the SIADH has not, to our knowledge, been reported in children after open heart surgery. In this communication, we describe a child in whom symptomatic hyponatremia was manifested clinically as acute brain syndrome[3] that occurred after surgical closure of an atrial septal defect.

REPORT OF A CASE

A 5-year-old girl was hospitalized for surgical closure of an atrial septal defect. Cardiac catheterization had revealed a secundum atrial septal defect with a pulmonary-to-systemic blood flow ratio of 2 and normal pulmonary artery pressure. On admission, the child appeared to be healthy, alert, and well oriented. Her temperature was 37 °C; blood pressure (BP), 100/70 mm Hg; heart rate, 85 beats per minute; and respirations, 26/min. Her weight was 21 kg and her height 110 cm. Neurologic examination revealed no abnormalities. A grade 3/4 blowing ejection systolic murmur was present at the left upper sternal border. The splitting of the second heart sound was wide and fixed. The ECG and chest roentgenogram were compatible with an atrial septal defect. Her hemoglobin concentration was 12.5 g/dL; serum sodium level, 140 mEq/L; serum potassium level, 4.1 mEq/L; serum chloride level, 100 mEq/L; serum bicarbonate level, 22 mmole/L; BUN level, 12 mg/dL; serum creatinine level, 0.6 mg/dL; serum calcium level, 9 mg/dL; and fasting blood glucose level, 60 mg/dL. Urinalysis results showed normal findings and a specific gravity of 1.020.

Surgery was performed using cardiopulmonary bypass at 32 °C. The extracorporeal circuit was primed with 1,500 mL of whole blood and 200 mL of lactated Ringer's solution. The total bypass time was 30 minutes. An atrial septal defect of the foramen ovalis type, 1.5 × 2 cm, was closed uneventfully. However, there was a 300-mL blood loss after closure of the atriotomy. This blood was adequately replaced, and the bleeding stopped after administration of 100 mL of fresh frozen plasma. The first postoperative day was uneventful. Her temperature was 37.2 °C; BP, 100/60 mm Hg; heart rate, 100 beats per minute; and respirations, 30/min. Serum electrolytes, BUN, and urinary specific gravity values were normal (Table).

On the second postoperative day, the patient suddenly became extremely irritable, uncooperative, and completely disoriented. Her temperature was 37.4 °C; heart rate, 110 beats per minute; respirations, 33/min; and BP, 110/70 mm Hg. The patient had not received barbiturates or morphine in the past 24 hours. Neurologic examination revealed no focal deficits. However, the deep tendon reflexes were diminished. There were no signs of dehydration or peripheral edema. The laboratory studies revealed the following values: serum sodium, 121 mEq/L; serum osmolality, 252 mOsm/kg; simultaneous urine osmolality, 850 mOsm/kg; and urine sodium, 170 mEq/L. The serum potassium level was 4.5 mEq/L; serum chloride level, 93 mEq/L; serum bicarbonate level, 20 mmole/L; BUN, 4 mg/dL; serum calcium level, 9 mg/dL; serum magnesium level, 1.5 mg/dL; and urinary specific gravity, 1.038. The blood glucose level was 180 mg/dL during the acute stage but the subsequent determinations were in the normal range. The SIADH was suspected, and the sodium requirements to correct the serum sodium level from 121 to 130 mEq/L were calculated (Δ serum sodium concentration × body weight [kg] × 0.6). A total of 113 mEq of sodium was administered as 3% sodium chloride solution. The patient's irritability disappeared within a period of ten minutes after 30 mL hypertonic saline solution was given. The remaining 100 mEq of sodium chloride was infused over the ensuing four hours. The fluid intake was restricted to 700 mL/sq m/24 hr plus replacement of nasogastric and chest tube drainage. The serum sodium level was restored to the normal 134 mEq/L, serum

Laboratory Data and Fluid Therapy*

	Postoperative Day				
	1	2	3	4	5
Serum sodium, mEq/L	140	121	142	140	138
Serum potassium, mEq/L	4.1	4.5	4.4	4.1	4.0
Serum chloride, mEq/L	100	93	101	100	99
Urine sodium, mEq/L	...	170	30	25	20
Urine potassium, mEq/L	...	90	17	15	15
Urine chloride, mEq/L	...	208	52	42	38
Serum osmolality, mOsm/kg	...	252	290	285	290
Urine osmolality, mOsm/kg	...	850	140	120	110
BUN, mg/dL	12	4	12	10	12
Sodium intake, mEq/24 hr	70	160	64	64	64
Urine, specific gravity	1.020	1.038	1.021	1.020	1.018
Fluid intake, mL/24 hr	1,200	855	850	850	850
Urine output, mL/24 hr	1,100	1,648	525	650	600

*Weight of patient, 21 kg; height, 110 cm.

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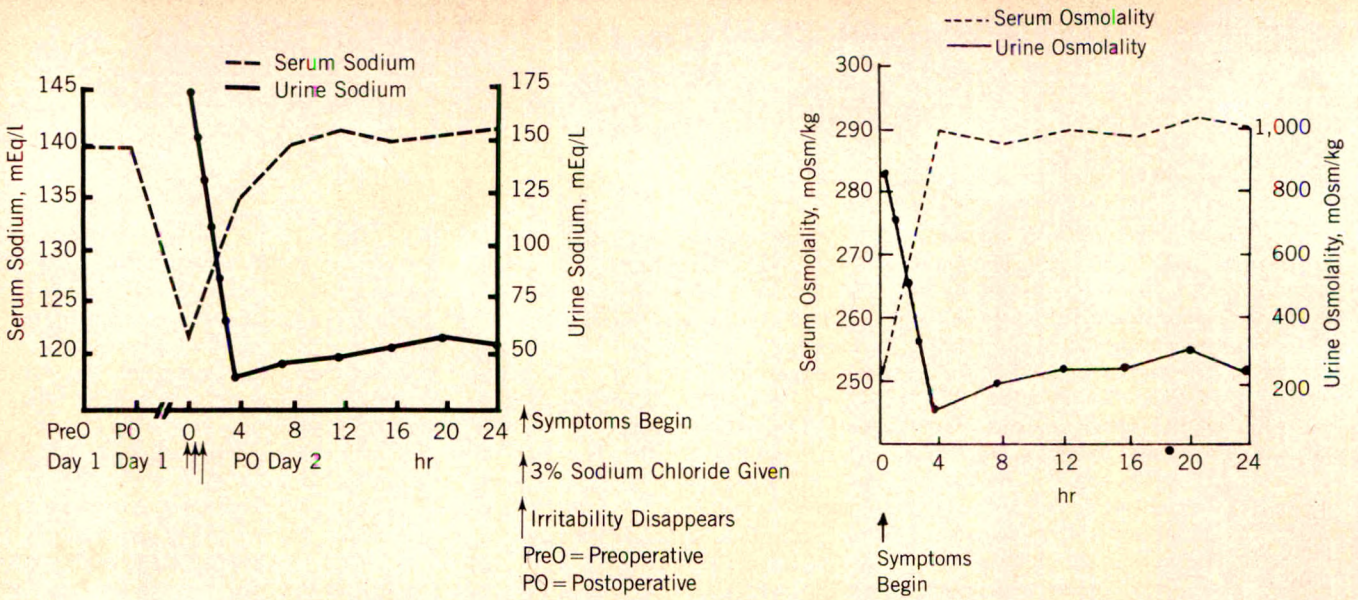

Left, Alterations in serum and urine sodium levels. Right, Osmolality after occurrence of symptoms. Laboratory measurements were obtained at four-hour intervals.

osmolality increased to 290 mOsm/kg, and urinary sodium excretion decreased to 30 mEq/L within a period of four hours. Her serum sodium level was maintained at 138 to 142 mEq/L by fluid restriction during the next five days. Fluid therapy and laboratory values are summarized in the Figure and Table.

COMMENT

The patient described in this case report had the hallmarks of the SIADH, including hyponatremia, serum hypoosmolality, and urine hyperosmolality with natriuresis. Her cerebral dysfunction was terminated on infusion of hypertonic saline solution. In addition, her serum sodium level increased and her clinical condition improved with fluid restriction. The presence of normal renal function, normal potassium levels, absence of dehydration or edema, and continuous favorable response to fluid restriction, further support the diagnosis of the SIADH in this 5-year-old child.

The antidiuretic hormone (ADH) is synthesized in the supraoptic nuclei of the hypothalamus and is carried to the posterior pituitary gland via the neurohypophysial tracts. The principal factors regulating release of ADH include the osmotic pressure of plasma and the circulating blood volume. The main action of ADH is to decrease renal excretion of free water. This mechanism normally maintains plasma osmolality within a narrow range. The change in plasma osmolality from full diuresis to the initiation of antidiuresis is approximately 2%.[4] It is generally believed that retention of water with low serum sodium levels, occurring postoperatively, results from inappropriate secretion of ADH. However, the mechanisms causing release of ADH postoperatively are not clearly understood.

The abrupt changes in hemodynamic equilibrium that occur with hemorrhage or total cardiopulmonary bypass have been associated with the SIADH.[5] Hypoperfusion resulting from hemorrhage could lead to prolongation of the half-life of ADH.[4] Blood loss can also trigger the volume and pressoreceptors, resulting in increased release of ADH.[4] In addition, hemorrhage could decrease the mean renal arterial pressure and increase renin secretion, leading to production of angiotensin II, which acts on the CNS and stimulates ADH production.[6] Factors often associated with surgery, such as stress, tissue trauma, visceral manipulation, narcotics, and anesthetic agents, stimulate the release of ADH.[7,8]

Inappropriate secretion of ADH, resulting from one or possibly a combination of the above multiple mechanisms, caused hyponatremia and initiated an acute brain syndrome[3] in this child. The clinical picture in this patient was highlighted by abrupt personality changes, extreme irritability, and transient loss of hearing and visual perception. This type of manifestation is often related to cerebrovascular accidents after cardiac surgery. An awareness of the SIADH is required to make a prompt diagnosis and to institute treatment. The potentially serious outcome of the SIADH warrants early recognition and appropriate measures. The possibility of the SIADH must be considered in children showing symptoms of cerebral dysfunction after open heart surgery.

References

1. Schwartz WB, Benneth W, Curelops S, et al: A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 23:529-542, 1957.

2. Bartter FC, Schwartz WB: The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 42:790-806, 1967.

3. Nicholi AM Jr: *The Harvard Guide to Modern Psychiatry*. Cambridge, Mass, The Belknap Press of Harvard University Press, 1978, pp 299-302.

4. Ganong WF: *Review of Medical Physiology*. Los Altos, Calif, Lange Publications, 1977, pp 164-169.

5. Shu'ayb WA, Moran WH Jr, Zimmermann B: Studies of the mechanism of antidiuretic hormone secretion and the postcommissurotomy dilutional syndrome. *Ann Surg* 162:690-699, 1965.

6. Ramsay DG, Ganong WF: CNS regulation of salt and water intake. *Hosp Pract* 12(3):63-66, 1977.

7. Deutsch S, Goldberg M, Dripps RD: Postoperative hyponatremia with the inappropriate release of antidiuretic hormone. *Anesthesiology* 27:250-256, 1966.

8. Moran WH Jr, Miltenberger FW, Shuayb WA, et al: The relationship of antidiuretic hormone secretion to surgical stress. *Surgery* 56:99-101, 1964.

Review

Acute Iron Poisoning

A Review

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The accidental ingestion of iron-containing preparations is relatively common in childhood, and intentional overdosage with iron is occasionally seen in adults. Though rarely fatal, the consequences of a substantial iron ingestion can result in profound mental retardation or death. The availability of deferoxamine mesylate, a specific and tenacious chelator of iron, and the necessity for its early administration demand that the physician be aware of a rational approach to the therapy for iron poisoning.

Owing to our current understanding of the pathophysiology of iron poisoning, we believe that the simultaneous oral and continuous intravenous (IV) administration of deferoxamine offers the most rational specific therapy for this condition. In this review we shall outline the clinical description, pathophysiology, and therapeutic regimens for acute iron intoxication. We have used this information to derive an approach we believe to be reasonable.

CLINICAL DESCRIPTION

The oral lethal dose (LD) of elemental iron is generally accepted to be 200 to 250 mg/kg, with the most common form of ferrous sulfate tablets being 20% elemental iron by weight.[1] However, this must not be used as an absolute value, since Arena states that as few as ten ferrous sulfate tablets (130 mg of elemental iron) have been fatal to a small child.[1]

The clinical description of acute iron poisoning has been well presented in several previous reviews.[2-8] Covey has emphasized four stages of iron poisoning.[9] The first stage occurs within six hours and is potentially, though rarely, fatal. It may include vomiting, an explosive diarrhea, irritability, abdominal pain, seizures, lethargy, and coma. Direct irritation of the gastrointestinal (GI) mucosa by iron tablets may lead to life-threatening acute hemorrhagic gastritis. Tachypnea, tachycardia, hypotension, and metabolic acidosis may occur. Other nonspecific laboratory findings during this stage may include a leukocytosis and hyperglycemia. During this first stage, the plasma iron level will be high after a significant ingestion.[5,10] However, due to the rapid clearance of iron from the plasma and its deposition in the liver, plasma iron levels may be deceptively low within a few hours of a substantial ingestion.[11,12] Consequently, at the time of initial clinical observation a severely toxic condition may be associated with only minimally elevated plasma iron levels.[3,4,12] The severity of the poisoning may be difficult to assess at this early stage. Westlin has emphasized the importance of shock or coma during this period as a grave prognostic index.[2,5]

After the first stage, there may be a period of deceptive quiescence. This period may extend up to 48 hours but is usually of less than 24 hours' duration.

A third stage may begin 12 to 48 hours after a substantial ingestion and may include shock, hypoperfusion, and hypoglycemia.[12,13] Again, it is important to note that serum iron levels may be normal during this stage.[2,3,5,14] Elevated levels of SGPT may reflect liver damage.[13,15] This stage appears to occur infrequently but its presence is ominous.

Late-appearing sequelae, constituting a fourth stage, may include pyloric or antral stenosis, hepatic cirrhosis, and CNS damage.[9,16]

PATHOPHYSIOLOGY

The pathophysiology of iron intoxication is complex and incompletely understood. Iron is absorbed by a first-order process even after massive doses.[7,12,17-20] The absorbed iron, possibly in the form of ferritin, causes a massive postarteriolar dilation with subsequent venous pooling. Total peripheral resistance increases to maintain a normal blood pressure (BP). A marked increase in capillary permeability leads to plasma loss and a rise in hematocrit level and in blood viscosity while blood volume, central venous pressure, and tissue perfusion decrease. Subsequently, the decreasing cardiac output leads to a state of shock and to cardiac failure, this state being reflected by an increased central venous pressure and tissue hypoperfusion that are associated with progressive cellular hypoxia and acidosis. The acidosis associated with iron poisoning may also be partially explained by the release of protons that are associated with the oxidation of the ferrous iron and subsequent hydration of the ferric iron.[7]

Once plasma transferrin has been saturated, absorbed iron is distributed into cells. The liver appears to be the primary site of uptake.[11] Although iron is initially taken up by Kupffer cells, it rapidly moves to hepatic parenchymal cells.[21-23] Electron microscopic studies localize the subcellular distribution of iron to the area of the mitochondrial cristae, the site of the electron transport system.[22,23] This occurs prior to morphologic or biochemical evidence of cellular damage. The mitochondrial localization appears to be critical to our understanding of many of the toxic effects of iron. Iron causes mitochondrial swelling, a rather nonspecific index of mitochondrial dysfunction.[23-27] One explanation for the mitochondrial dysfunction that is produced by iron is provided by the known action of ferrous ions as potent catalysts of lipid peroxidation. Experimental evidence for this action includes the thiobarbiturate acid reaction, the production of malonaldehyde, and the increased consumption of oxygen.[24,25,28-33] Lipid peroxidation induced by ferrous ions has been associated with marked alterations in mitochondrial membrane composition and in functions of both the Krebs cycle and the electron transport system.[29] Mitochondria may be particularly susceptible to lipid peroxidation as a result of the high concentration of polyunsaturated fatty acids in their membranes.[34] Double carbon bonds in the polyunsaturated lipids can be disrupted by reacting with the free-radical singlet oxygen. Lipid peroxidation catalyzed by ferrous iron may thus change membrane permeability so as to allow rapid intramitochondrial accumulation of additional iron and may directly alter the steric configuration of the mitochondrial membrane, which is essential for the proper functioning of the electron

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transport system and thus for aerobic respiration. The potential for biologic toxicity of lipid peroxidation has been increasingly recognized. The pulmonary sequelae of oxygen toxicity may be mediated through lipid peroxidation.[35] The roles of iron and vitamin E supplements as causes and treatments, respectively, of the anemia of prematurity have been investigated.[36,37] There appears to be an age-dependent development of biologic protective mechanisms (superoxide dismutase) in many tissues, including the lung and the liver.[35,38] Thus, if lipid peroxidation is an important contributing mechanism in iron's toxicity, the younger patient may be at greater risk. Also, it would be predicted that iron's toxicity would be manifested depending on the relative concentrations of iron and polyunsaturated lipids and that it would result in multiorgan dysfunction.

Another plausible explanation for the mitochondrial damage produced by iron is based on the ability of iron to act as an electron sink, resulting in the shunting of electrons away from the electron transport system.[39] The reduction of ferric iron, the predominant ionic form of iron at a pH of 7, by an enzyme located on the inner mitochondrial membrane normally functions to provide ferrous iron for insertion into protoporphyrin IX. In the presence of an iron overload, this same enzyme might reduce the massive amount of excess ferric iron to ferrous iron, which in turn would be promptly oxidized back to the ferric state in the presence of intramitochondrial oxygen. Thermodynamic considerations of this system would favor the shunting of electrons away from the electron transport system, thereby diminishing oxidative phosphorylation and reducing the adenosine triphosphate (ATP) that is generated.[39] If this mechanism were operative, experimental observations would demonstrate oxygen uptake without ATP formation. The same finding could also be interpreted as an uncoupling of mitochondrial oxidative phosphorylation in which oxygen would also be used without ATP being formed.[24,30] A number of observations of iron metabolism in normal and in iron-intoxicated states are consistent with the hypothesis that iron acts as an electron sink.[23,40] The end result of this process would be cellular dysfunction and ultimately death due to the impaired generation of ATP. The fact that absorbed iron can neither be detoxified nor rapidly excreted markedly enhances susceptibility to acute iron poisoning.[41]

THERAPY

As a common denominator in the therapy of most iron poisonings, consideration should be given to the prevention of continued absorption, the enhancement of elimination, and the prevention or reversal of the cellular pathophysiology. With respect to iron poisoning, the chelating agent, deferoxamine, would appear to beneficially influence each of these processes. Deferoxamine is a highly specific chelator of ferric (Fe^{3+}) iron with an affinity for iron (10^{31}) that is more than ten times greater than any other known chelator of iron. Deferoxamine has an affinity constant for iron two orders of magnitude greater than does transferrin.[42-44] One hundred milligrams of deferoxamine is capable of binding 9.35 mg of elemental iron.[45]

Deferoxamine—Mechanism of Action

The protective effect of deferoxamine given orally appears to be due to its ability to bind iron in the gut and thus prevent absorption of the ingested iron. The usual explanation given for the effectiveness of parenteral deferoxamine involves the enhancement of iron elimination through the formation of the water-soluble, renally excreted ferrioxamine. Though this may be of major importance in the effectiveness of parenteral deferoxamine, several reports suggest that the urinary elimination of iron may be insufficient to account for the drug's effectiveness.[6,46,47] Thus it may be that deferoxamine also exerts a protective effect at the cellular level.[48] The chelation of iron by deferoxamine in the extracellular space may limit the entry of iron into cells by virtue of the decreased membrane permeability of ferrioxamine, thus preventing an intracellular toxic state. Second, deferoxamine could enter cells and chelate extramitochondrial iron.[45] The ferrioxamine that is formed might well remain outside of the mitochondria, thus preventing the movement of iron to the potentially critical area of the inner mitochondrial membrane.[40] Third, if deferoxamine does enter mitochondria, then intramitochondrial deferoxamine could bind intramitochondrial iron and might limit mitochondrial injury that results from lipid peroxidation.[33] This last explanation would not be applicable if the mechanism of iron toxicity involves the shunt mechanism mentioned above, since ferrioxamine has been shown to be capable of providing iron as a usable substrate for the reducing enzyme of the inner mitochondrial membrane.[40]

Deferoxamine—Pharmacokinetics

The rational use of deferoxamine requires an understanding of its pharmacology. Deferoxamine complexes preferentially, if not exclusively, with the ferric ion.[43] Most commonly, medicinal iron is in the ferrous ion because it is better absorbed.[17] The rate and extent of the chelation of iron by deferoxamine can be markedly increased by changing the pH of the medium from 2 to 6. This increase has been attributed to the rapid oxidation of the ferrous to the ferric ion accompanying the increase in pH.[43] The product of the chelation of ferric iron with deferoxamine, ferrioxamine, is quite stable at physiologic pH.

Deferoxamine is poorly absorbed when administered orally and thus might be expected to remain in the GI tract and bind unabsorbed iron.[44,45] Conclusive studies on the fate of the bound iron, ferrioxamine, in the GI tract are not, to our knowledge, available. However, Keberle has stated that ferrioxamine is poorly absorbed from the gut,[44] and Misra et al have confirmed this in vitro.[49] After the oral administration of crystalline ferrioxamine to dogs, Whitten et al reported the renal excretion of 3.4% to 22.2% of the dose, this suggesting some absorption of the ferrioxamine.[19] The clinically relevant questions, however, are whether or not oral deferoxamine will decrease the absorption of orally administered iron and whether the toxicity of the chelate thus formed is substantially less than that of the free iron. Evidence for a decrease in absorption of iron with oral deferoxamine has been provided by Keberle,[44] by Balcerzak et al,[50] by Bannerman and Malpas,[51] and by Hwang and Brown.[52] In addition, several studies have demonstrated the marked reduction in mortality in experimental iron poisoning when associated with the oral use of deferoxamine.[45,53]

Once absorbed, deferoxamine is distributed into a volume equal to 60% of the body weight. Ferrioxamine, on the other hand, is distributed into a volume corresponding to only 20% of the body weight.[44,54,55] This would suggest that ferrioxamine remains in an extracellular compartment, whereas deferoxamine may enter cells. In vitro experiments have demonstrated that ferrioxamine is excluded from the mitochondria.[40]

Deferoxamine is rapidly metabolized to inactive products by plasma as well as by other tissues.[42,44,54,56] After IV administration to nephrectomized dogs, the serum half-life of deferoxamine is about one hour.[42,54] This rapid elimination of deferoxamine may be important in the construction of an adequate dosage regimen. Ferrioxamine, on the other hand, is very slowly metabolized and is eliminated primarily unchanged in urine, with a clearance approximating the glomerular filtration rate.[54,56] In normal dogs, 94% of an intrave-

nously administered dose is recovered in the urine within five hours, while in nephrectomized dogs the serum half-life is markedly prolonged, suggesting a lack of other routes of elimination.[54] Ferrioxamine is a dialyzable, water-soluble complex.[19]

Deferoxamine—Toxicity

The toxicity of deferoxamine, if properly used, is minimal. It includes GI discomfort after oral administration and hypotension with excessively rapid IV administration of large doses. The toxicity of ferrioxamine has not, to our knowledge, been systematically studied, but some experimental data suggest that the toxicity of ferrioxamine is less than that of iron itself.[19]

Deferoxamine—Efficacy

Ultimately, the clinical usefulness of deferoxamine in acute iron intoxication rests on the demonstration of its therapeutic effectiveness. Since it is exceedingly difficult to acquire this evidence in human iron intoxication, we must rely heavily on studies in experimental animals.

Published evidence for the effectiveness of parenterally administered deferoxamine is meager. Tripod[53] has shown the mortality to be decreased from 75% to 20% to 30% if subcutaneous deferoxamine is given between 30 and 120 minutes after oral iron. Hosking has demonstrated that the dose of iron necessary to kill 50% of his mice was increased fivefold when the animals were treated with intramuscular (IM) deferoxamine.[57] On the other hand, Whitten has reported that the use of IV deferoxamine failed to provide protection for orally poisoned dogs.[3]

A sizeable amount of data would appear to support the efficacy of orally administered deferoxamine. Several human studies, using non-LDs of iron, have demonstrated the ability of oral deferoxamine to diminish the absorption of oral iron.[50,52] Similar results have been reported in experimental animals.[44,51] Oral administration of deferoxamine protected 75% of mice from an oral iron dose that should have been lethal to 75%.[53] Moeschlin and Schnider have demonstrated a 60% survival rate in guinea pigs that were given a dose of iron calculated to kill 100% of the animals.[45] Both of these reports emphasized the importance of providing the deferoxamine soon after the iron has been ingested since efficacy decreased with time after ingestion.

A lack of effectiveness of oral deferoxamine has been suggested by Whitten, who has shown a lack of protection in four dogs given LDs of iron.[3] After a similar dose of iron was given orally to five dogs as the crystalline ferrioxamine complex, all were alive after 24 hours and only two had died after 48 hours. Fourteen control dogs given the same dose of free iron had died within ten hours. These latter experiments appear to be the basis for the belief that oral deferoxamine is contraindicated in iron poisoning. On the contrary, we believe that these results should be interpreted as evidence in favor of the therapeutic effectiveness of oral deferoxamine. Thus, a 60% survival rate was realized when an otherwise LD of iron was given as the chelate.

Since both oral and parenteral modes of administration appear to have some degree of therapeutic value, a combination of these two routes would seem to be worthy of attention. The only experimental evidence that we have been able to find relevant to this approach is provided by Whitten et al, who have shown a marked increase in survival in dogs that had been treated with combined oral and IV deferoxamine in spite of the lack of protection afforded by either method alone.[3,19]

ADJUNCTIVE THERAPY

Various modes of adjunctive therapy have also been advocated without good experimental data to show clinical efficacy. Bicarbonate will form insoluble aggregates of ferrous carbonate and impede iron absorption from physiologic doses of iron in man.[17] The $NaHCO_3$, given either orally or intraperitoneally, greatly decreased mortality in mice when compared with untreated controls.[57] Oral phosphates (eg, sodium biphosphate) have also been advocated on the basis that they, too, will form insoluble aggregates.[4] Although this decreases the absorption after small doses of iron, its effectiveness has never been demonstrated after toxic doses.

Exchange transfusion has been suggested as a method for the enhancement of iron elimination.[46] In view of the rapid intracellular movement of iron, exchange transfusion would not seem to be an efficient therapeutic modality. The single study, in our search of the literature, of exchange transfusion in iron poisoning (in dogs) has documented the inefficiency of this maneuver.[46] If the pathophysiologic effect of iron poisoning involves the generation of free radicals initiated by ferrous ions, then it might be possible to aim therapy at the systems involved in the initiation and propagation of free radicals and lipid peroxidation. One might provide an antioxidant or a free-radical scavenger such as vitamin E, ethoxyquin, or a sulfhydryl-containing agent such as penicillamine or mercaptamine (cysteamine). Remarkably similar morphologic changes have been found in both vitamin E-deficient and iron-overloaded animals.[58,59] At a biochemical level, many of the abnormalities of cellular respiration found in iron-poisoned mitochondria are also found in mitochondria from vitamin E-deficient animals. The addition of vitamin E to these in vitro preparations reverses the iron-induced morphologic abnormalities and restores the normal respiratory control.[24,25,34] Furthermore, vitamin E-deficient animals show a markedly enhanced susceptibility to iron poisoning,[60,61] and chronically iron-poisoned animals that are treated with large doses of vitamin E have demonstrated prevention of some pathologic changes.[62-64] Two patients with iron poisoning were allegedly successfully treated with vitamin E in 1951.[65] We emphasize that we are not advocating the use of antioxidants or sulfhydryl-containing compounds for iron poisoning but merely raising these possibilities as speculations.

RECOMMENDATIONS

Based on the information just reviewed, our belief is that a rational therapeutic approach to acute iron poisoning is possible (Table). While recognizing that mortality and substantial morbidity are infrequent in comparison with the total number of patients with a history of iron ingestion, we believe that the initial management suggested is justified in view of the potential seriousness of this poisoning.

All patients arriving with a history of iron ingestion should be given an IM injection of 2 g of deferoxamine mesylate. Emesis with ipecac should be immediately induced if the patient is conscious and a gag reflex is present. The vomitus should be examined for evidence of iron tablets. After emesis, gastric lavage should be performed with a solution containing 2 g of deferoxamine mesylate per liter of water and sufficient $NaHCO_3$ to alkalinize ($pH > 5$) the gastric contents and increase the deferoxamine complexation of iron.[66] After lavage, deferoxamine mesylate (10 g in 50 mL of water; a dose that should complex a substantial percentage of most ingestions in small children) should be left in the stomach with sufficient $NaHCO_3$ added so that the aspirated gastric contents will have a pH greater than 5. This is easily checked with pH paper.

An elevated total serum or plasma

Treatment of Iron Poisoning for All Patients With a History of Excessive Iron Ingestion

A. Perform the following:
   1. Give deferoxamine (2 g intramuscularly, unless the patient is in shock)
   2. Give ipecac (if patient is conscious and if gag reflex is present)
   3. Lavage (after emesis) with deferoxamine (2 g in 1 L of water containing enough $NaHCO_3$ to "alkalinize" [pH > 5] the gastric contents)
   4. Leave in stomach (via lavage tube) deferoxamine (10 g in 50 mL of water with sufficient $NaHCO_3$ to alkalinize [pH > 5] the gastric contents)
   5. Provide intravenous (IV) fluids as necessary
   6. Obtain a serum iron level
   7. Obtain an abdominal roentgenogram

B. Consider the following three conditions and initiate action as follows (C, D):
   1. Signs or symptoms by history or observation
   2. *Vin rosé*-colored urine with good urine output
   3. Evidence of iron tablets by adbominal roentgenogram

C. If all three conditions are negative for six hours of observation, then discharge after six hours

D. If any of the three conditions is positive, then admit for further treatment as follows:
   1. Give deferoxamine by continuous IV infusion (15 mg/kg/hr)
   2. Monitor and support intravascular volume and tissue perfusion
   3. Continue therapy until urine is clear of *vin rosé* color and patient is asymptomatic for at least 24 hours
   4. Discharge patient
   5. Perform follow-up examination

iron level can be a useful index of significant ingestion. However, it is important to reemphasize that, due to the rapid clearance of free iron, severely toxic conditions can be associated with only minimally elevated plasma iron levels.[2,5,10,13] In animal studies with LDs of oral iron, the serum iron level one hour after ingestion ranged from 800 to 13,800 μg/dL.[3] When serial serum iron levels were studied, death was usually associated with peak serum iron levels over 1,000 μg/dL, but it was also associated with serum iron levels less than 500 μg/dL as early as three hours after ingestion.[10] Peak serum iron levels usually occur between two and four hours after ingestion.[3,12,20] Clinical reports have also included instances of serious toxicity with serum iron levels below 300 μg/dL.[2,3,10] In view of these data, whereas it seems reasonable that a serum iron level over 300 μg/dL should be of concern, a level less than 300 μg/dL does not rule out serious intoxication. It is important to remember that colorimetric methods for determining serum iron levels can give falsely low values in the presence of deferoxamine[67] unless a strong reducing agent is added to the assay system.[68]

Fluids should be given to ensure a good urinary output and any urine passed should be observed for a *vin rosé* color, which indicates iron as ferrioxamine that has been filtered into the urine. The initial urine obtained may reflect residual urine formed prior to the administration of the deferoxamine and thus may be negative in the face of a serious ingestion.

A roentgenogram of the abdomen may be useful in detecting evidence of residual iron tablets.

If, six hours after ingestion, the patient remains asymptomatic by history and observation; there is a good urinary output with absence of any *vin rosé* color; and the abdominal roentgenogram does not show residual iron tablets, then it is likely that the patient can be safely sent home.

The child who at any time, by history or observation, is considered to exhibit signs or symptoms of acute iron poisoning (see "Clinical Description"), passes a *vin rosé*-colored urine, or has an abnormal abdominal roentgenogram for iron tablets should be started on a continuous IV infusion of deferoxamine at 15 mg/kg/hr in either saline or lactated Ringer's solution. In view of the possible intracellular action of deferoxamine, it seems reasonable to continue treatment until after the *vin rosé* color of the urine has been clear and the child is without signs or symptoms of iron poisoning for 24 hours. In the event of ingestion of enteric coated tablets and/or an abnormal abdominal roentgenogram, even though the urine is initially clear, it is probably safest to continue IV deferoxamine for 24 hours.

In addition to the above recommendations, we cannot stress too strongly the importance of careful monitoring and vigilance in maintaining optimal intravascular volume and tissue perfusion. In the markedly symptomatic child, particular attention should be paid to adequately replacing "third space" fluid losses. In our experience with significant iron intoxications both in children and in animal studies, large volumes of colloid and crystalloid replacement are necessary to maintain perfusion to critical organ beds. With large GI losses that may not be immediately appreciated, the child who is clinically manifesting any marked signs of a toxic condition deserves immediate admission to an intensive care unit. Placement of adequate catheters for monitoring and for infusion, as would be done in any patient at considerable risk of shock, should be carried out immediately. A separate IV line should be established specifically for deferoxamine administration so that fluid boluses can be given without fear of rapidly infusing deferoxamine.

In the unfortunate child who, despite optimal support and management, manifests oliguria or anuria as associated with shock or coma, thereby indicating a severe intoxication, hemodialysis should be considered while continuing IV deferoxamine in view of ferrioxamine's ability to be dialyzed.[19] Peritoneal dialysis in the face of shock or hypoperfusion would likely be ineffective.

In those children who experience acute iron poisoning, it is important to plan adequate follow-up for the potential sequelae outlined previously. Additionally, there may occur the paradox of iron deficiency anemia after acute iron poisoning (oral communication, William H. Zinkham, MD, December 1963). This may reflect a combination of GI losses and chelation of iron stores by deferoxamine.

Finally, we wish to emphasize that an ounce of prevention is worth more than a pound of deferoxamine.

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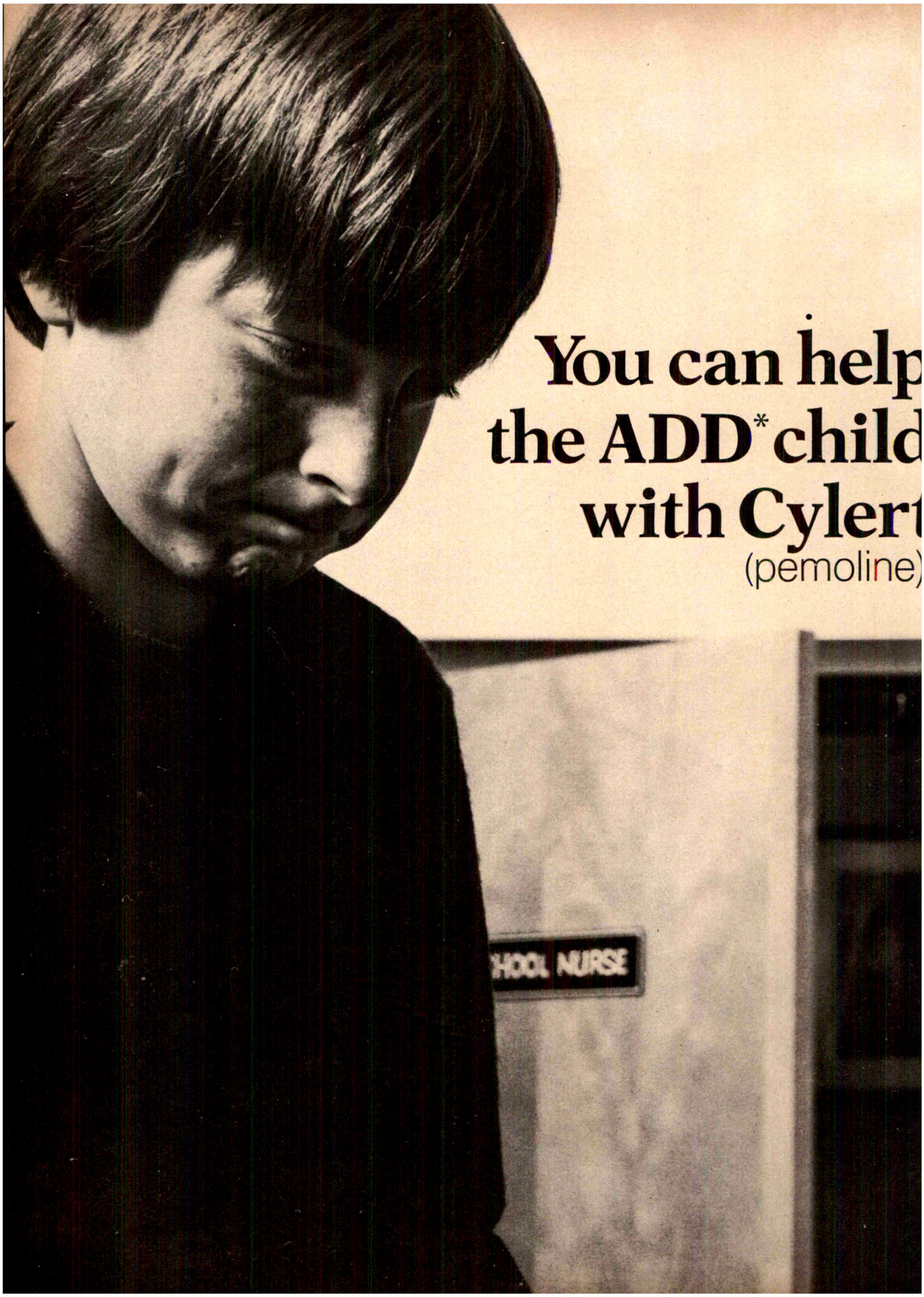
References

1. Arena JM: *Poisoning*, ed 2. Springfield, Ill, Charles C Thomas Publisher, 1970, pp 349-353.
2. Westlin WF: Deferoxamine in the treatment of acute iron poisoning: Clinical experience with 172 children. *Clin Pediatr* 5:531-535, 1966.
3. Whitten CF, Gibson GW, Good MH, et al: Studies in acute iron poisoning: I. Deferoxamine in the treatment of acute iron poisoning: Clinical observations, experimental studies, and theoretical considerations. *Pediatrics* 36:322-335, 1965.
4. Fischer DS, Parkman R, Finch SC: Acute iron poisoning in children: The problem of appropriate therapy. *JAMA* 218:1179-1184, 1971.
5. Westlin WF: Deferoxamine as a chelating agent. *Clin Toxicol* 4:597-602, 1971.
6. McEnery JT, Greengard J: Treatment of acute iron ingestion with deferoxamine in 20 children. *J Pediatr* 68:773-779, 1966.
7. Whitten CF, Brough AJ: The pathophysiology of acute iron poisoning. *Clin Toxicol* 4:585-595, 1971.
8. Barker GA, Brown TCK, Hosking CS: Acute iron poisoning: Clinical features and management. *Anaesth Intensive Care* 4:345-350, 1974.
9. Covey TJ: Ferrous sulfate poisoning: A review, case summaries, and therapeutic regimen. *J Pediatr* 64:218-226, 1964.
10. James JA: Acute iron poisoning: Assessment of severity and prognosis. *J Pediatr* 77:117-119, 1970.
11. Wheby MS, Jones LG: Role of transferrin in iron absorption. *J Clin Invest* 42:1007-1016, 1963.
12. Reissmann KR, Coleman TJ, Budai BS, et al: Acute intestinal iron intoxication: I. Iron absorption, serum iron, and autopsy findings. *Blood* 10:35-45, 1955.
13. Barr DGD, Fraser DKB: Acute iron poisoning in children: Role of chelating agents. *Br Med J* 1:737-741, 1968.
14. McEnery JT: Hospital management of acute iron ingestion. *Clin Toxicol* 4:603-613, 1971.
15. Witzleben CL: The pathogenesis of iron hepatotoxicity. *Ann NY Acad Sci* 165:105-110, 1969.
16. Gandhi RK, Robarts FH: Hour-glass stricture of the stomach and pyloric stenosis due to ferrous sulfate poisoning. *Br J Surg* 49:613-617, 1962.
17. Murray MJ: Iron absorption. *Clin Toxicol* 4:545-558, 1971.
18. Fairbanks VF, Fahey JL, Beutler E: Clinical disorders of iron metabolism, in *Clinical Disorders of Iron Metabolism*, ed 2. New York, Grune & Stratton Inc, 1971, pp 42-127.
19. Whitten CF, Chen YC, Gibson GW: Studies in acute iron poisoning: II. Further observations on deferoxamine in the treatment of acute iron poisoning. *Pediatrics* 38:102-110, 1966.
20. Whitten CF, Chen YC, Gibson GW: Studies in acute iron poisoning: III. The hemodynamic alterations in acute experimental iron poisoning. *Pediatr Res* 2:479-485, 1978.
21. Witzleben CL, Chaffey NJ: Acute ferrous sulfate poisoning: A histochemical study of its effect on the liver. *Arch Pathol Lab Med* 82:454-461, 1966.
22. Witzleben CL: An electron microscopic study of ferrous sulfate-induced liver damage. *Am J Pathol* 49:1053-1068, 1966.
23. Ganote CE, Nahara G: Acute ferrous sulfate hepatotoxicity in rats: An electron microscopic and biochemical study. *Lab Invest* 28:426-436, 1973.
24. Hunter FE Jr, Gebicki JM, Hoffstein PE, et al: Swelling and lysis of rat liver mitochondria induced by ferrous ions. *J Biol Chem* 238:828-835, 1963.
25. Hoffstein PE, Hunter FE Jr, Gebicki JM, et al: Formation of "lipid peroxide" under conditions which lead to swelling and lysis of rat liver mitochondria. *Biochem Biophys Res Commun* 7:276-280, 1962.
26. Corwin LM, Lipsett MN: Studies on stability of rat liver mitochondria. *J Biol Chem* 234:2453-2458, 1959.
27. Lehninger AL: Water uptake and extrusion by mitochondria in relation to oxidative phosphorylation. *Physiol Rev* 42:467-517, 1962.
28. Hochstein P, Ernster L: Microsomal peroxidation of lipids and its possible role in cellular injury, in DeReuck AVS, Knight J (eds): *Cellular Injury*. Boston, Little Brown & Co, 1964, pp 123-135.
29. Gruger EH Jr, Tappel AL: Reactions of biological antioxidants: I. Fe(III)-catalyzed reactions of lipid hydroperoxides with alpha-tocopherol. *Lipids* 5:326-331, 1970.
30. McKnight RC, Hunter FE Jr: Mitochondrial membrane ghosts produced by lipid peroxidation induced by ferrous ion. *J Biol Chem* 241:2757-2765, 1966.
31. Wills ED: Lipid peroxide formation in microsomes: General considerations. *Biochem J* 113:315-324, 1969.
32. Barbar AA: Lipid peroxidation in rat tissue homogenates: Interaction of iron and ascorbic acid as the normal catalytic mechanism. *Lipids* 1:146-151, 1966.
33. Wills ED: Lipid peroxide formation in microsomes: The role of nonhaem iron. *Biochem J* 113:325-332, 1969.
34. McGray PB, Pfeifer PM, Stipe WH: Vitamin E protection of membrane lipids during electron transport functions. *Ann NY Acad Sci* 203:62-73, 1972.
35. Mustafa MG, Tierney DF: Biochemical and metabolic changes in the lung with oxygen, ozone, and nitrogen dioxide toxicity. *Am Rev Respir Dis* 118:1061-1090, 1978.
36. Graeber JE, Williams ML, Oski FA: The use of intramuscular vitamin E in the premature infant. *J Pediatr* 90:282-284, 1977.
37. Roders MK, Glende EA, Recknagel RO: NADPH-dependent microsomal lipid peroxidation and the problem of pathological action at a distance. *Biochem Pharmacol* 27:437-443, 1978.
38. Yoshiokai T, Utsumi K, Sekibu K: Superoxide dismutase activity and lipid peroxidation of the rat liver during development. *Biol Neonate* 32:147-153, 1977.
39. Robotham JL, Troxler RF, Lietman PS: Iron poisoning: Another energy crisis. *Lancet* 2:664-665, 1974.
40. Barnes R, Connelly JL, Jones OTG: The utilization of iron and its complexes by mammalian mitochondria. *Biochem J* 128:1043-1055, 1972.
41. Trump BF, Valigrosky JM, Arstila AU, et al: The relationship of intracellular pathways of iron metabolism to cellular iron overload and the iron storage diseases. *Am J Pathol* 72:295-336, 1973.
42. Schubert J: The chemical basis of chelation, in Gross F (ed): *Iron Metabolism: International Symposium on Iron Metabolism*. Berlin, Springer-Verlag, 1964, pp 466-496.
43. Goodwin JF, Whitten CF: Chelation of ferrous sulfate solution by deferoxamine B. *Nature* 205:281-283, 1965.
44. Keberle H: The biochemistry of deferoxamine and its relation to iron metabolism. *Ann NY Acad Sci* 119:758-768, 1964.
45. Moeschlin S, Schnider U: Treatment of primary and secondary hemochromatosis and acute iron poisoning with a new, potent, iron-eliminating agent (deferoxamine-B). *N Engl J Med* 269:57-61, 1963.
46. Movassaghi N, Purugganan GG, Leikin S: Comparison of exchange transfusion and deferoxamine in the treatment of acute iron poisoning. *J Pediatr* 75:604-608, 1969.
47. Leikin S, Vossough P, Mochir-Fatemi F: Chelation therapy in acute iron poisoning. *J Pediatr* 71:425-430, 1967.
48. Lipschitz DA, Dugard J, Simon MO, et al: The site of action of deferoxamine. *Br J Haematol* 20:395-404, 1971.
49. Misra AL, Hunger A, Keberle H: The passage of drugs across the rat intestine in vitro. *J Pharm Pharmacol* 18:246-251, 1966.
50. Balcerzak SP, Jensen WN, Pollack S: Mechanism of action of deferoxamine on iron absorption. *Scand J Haematol* 3:205-212, 1966.
51. Bannerman RM, Malpas JS: Studies on deferoxamine in relation to absorption of iron. *Br J Haematol* 11:15-20, 1965.
52. Hwang YF, Brown EB: Effect of deferoxamine on iron absorption. *Lancet* 50:135-137, 1965.
53. Tripod J: A pharmacological comparison at the binding of iron and other metals, in Gross F (ed): *Iron Metabolism: International Symposium on Iron Metabolism*. Berlin, Springer-Verlag, 1964, pp 503-524.
54. Peters G, Keberle H, Schmid K, et al: Distribution and renal excretion of desferrioxamine and ferrioxamine in the dog and in the rat. *Biochem Pharmacol* 15:93-109, 1966.
55. Brown EB, Hwang YF, Allgood JW: Studies on the site of action of deferoxamine. *J Lab Clin Med* 69:382-404, 1967.
56. Meyer-Brunot HG, Keberle H: The metabolism of deferoxamine-B and ferrioxamine-B. *Biochem Pharmacol* 16:527-535, 1967.
57. Hosking CS: A pharmacologic investigation of acute iron poisoning and its treatment. *Aust Paediatr J* 6:92-96, 1970.
58. Diplock AT, Green J, Bunyan J, et al: Vitamin E and stress: Iron overloading and the metabolism of D-alpha-tocopherol in the rat. *Br J Nutr* 21:725-730, 1967.
59. Goldberg L, Smith JD: Vitamin A and E deficiencies in relation to iron overloading in the rat. *J Pathol Bacteriol* 80:173-180, 1960.
60. Cambridge GW, McDonald FF: The influence of diet on the acute toxicity of injectable iron preparations in the mouse. *Br J Pharm Chemother* 27:114-119, 1966.
61. King JT, Lee YCP, Visscher MB: Relationship between vitamin E and dietary minerals in mouse 'paralysis'. *Proc Soc Exp Biol Med* 88:406-409, 1955.
62. Tollerz G, Lanner N: Protection against iron toxicity in vitamin E deficient piglet and mice by vitamin E and synthetic antioxidants. *Nature* 201:846-847, 1964.
63. Green J: Vitamin E and the biological antioxidant theory. *Ann NY Acad Sci* 203:29-44, 1972.
64. Goldberg L, Smith JP: Changes associated with the accumulation of excessive amounts of iron in certain organs of the rat. *Br J Exp Pathol* 39:59-73, 1958.
65. Spencer IOB: Ferrous sulfate poisoning in children. *Br Med J* 2:1112-1117, 1951.
66. Matthew H, Lawson AAH: *Treatment of Common Acute Poisonings*. London, Churchill Livingstone, 1975, pp 93-95.
67. Helfer RE, Rodgerson DO: The effect of deferoxamine on the determination of serum iron and iron binding capacity. *J Pediatr* 68:804-806, 1966.
68. Gesvirtz NR, Wasserman LR: The measurement of iron and iron binding capacity in plasma containing deferoxamine. *J Pediatr* 68:802-804, 1966.
69. Propper RD, Shurin SB, Nathan DG: Reassessment of the use of deferoxamine B in iron overload. *N Engl J Med* 294:1421-1423, 1976.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CYLERT (pemoline) is supplied as tablets for oral administration.

CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

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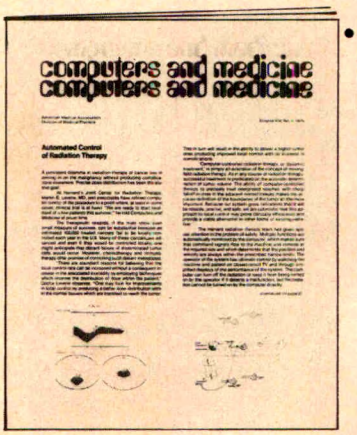

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Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD;
Contributed by Emanuel Tirosh, MD; Daniel Hardoff, MD; Rachel Friedman-Birnbaum, MD

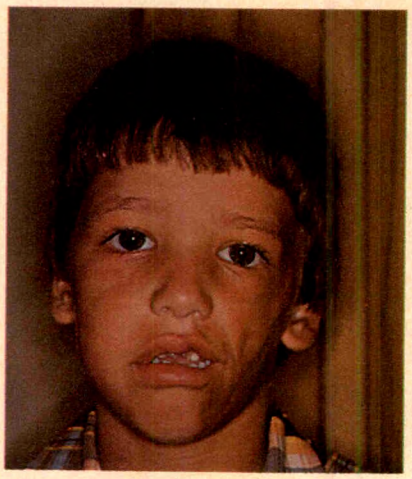

Figure 1.

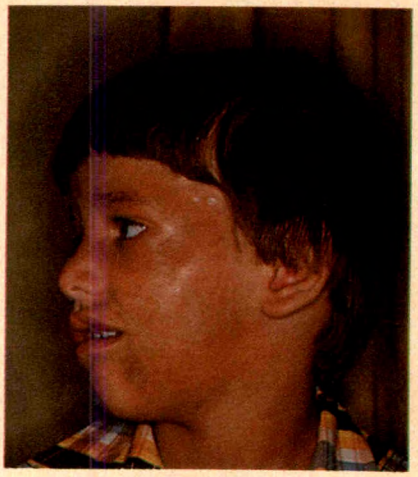

Figure 2.

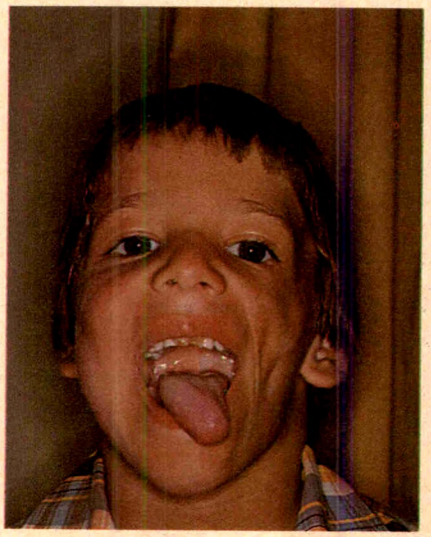

Figure 3.

From the Department of Pediatrics (Drs Tirosh and Hardoff), Rothschild's University Hospital, and the Department of Dermatology (Dr Friedman-Birnbaum), Rambam's University Hospital, Haifa, Israel.

Reprint requests to Boston Floating Hospital, 20 Ash St, Boston, MA 02111 (Dr Gellis).

Denouement and Discussion

Hemifacial Atrophy (Romberg's Syndrome)

Fig 1.—Characteristic facial appearance with atrophy limited to one side.

Fig 2.—Brown pigmentation and sparsity of hair on same side as atrophy.

Fig 3.—Hemiatrophy of tongue that is deviated toward facial lesion.

Manifestations

Major manifestations include progressive atrophy of the face accompanied by seizures, trigeminal neuralgia, and increased pigmentation of the overlying skin.

The atrophy involves skin, subcutaneous tissue, muscles, and occasionally cartilage and bone. It usually appears by age 10 and, initially, frequently involves the temporal or buccinator muscles; it then extends to the brow, angle of the mouth, neck; and subsequently it may involve other parts of the body. The left side is more frequently affected than the right. The atrophy continues for approximately three years and then becomes nonprogressive. Changes in the hair may precede the skin findings and include alopecia and poliosis. Eye abnormalities, frequently secondary to the atrophy, may occur and consist of enophthalmos, outward slanting of the outer canthus, muscular paralyses, inflammation of the eyes, heterochromia of the iris, and Horner's syndrome.

Epilepsy, mainly of the Jacksonian type, is a common neurologic occurrence and usually appears late. Trigeminal neuralgia and migraine headaches also occur.

Roentgenograms of the jaw show the bodies of the ramus and mandible to be shorter on the affected side. The teeth on the involved side may be delayed in erupting and have atrophic roots.

Differential diagnosis includes scleroderma, fat necrosis, hemifacial microsomia, and oculoauriculovertebral dysplasia (Goldenhar's syndrome).

Genetics

The majority of cases have been sporadic although there have been a few familial cases reported. A history of facial trauma has been reported in some affected individuals.

Treatment

Since it is a self-limiting condition, treatment is mainly symptomatic. Plastic surgery is frequently helpful.

References

1. Gorlin RJ, Pindborg JJ, Cohen MM: Hemifacial atrophy, in: *Syndromes of the Head and Neck*, ed 2. New York, McGraw-Hill Book Co Inc, 1976, pp 341-343.
2. Glass D: Hemifacial atrophy. *Br J Oral Surg* 1:194-199, 1963-1964.
3. Crikelair GF, Moss ML, Khuri A: Facial hemiatrophy. *Plast Recon Surg* 29:5-13, 1962.

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Radiological Case of the Month

Lionel W. Young, MD; Contributed by Kong Meng Tan, MD

A17-year-old high school football player complained of pain involving his left hip after a game. He was referred to the orthopedic department, Kaiser-Permanente Medical Center, Richmond, Calif, after roentgenograms (anteroposterior pelvis, Fig 1) of his left hip had been reviewed by the radiologist and the boy's pediatrician. He had no previous complaints or hospital admissions. No laboratory examinations were obtained.

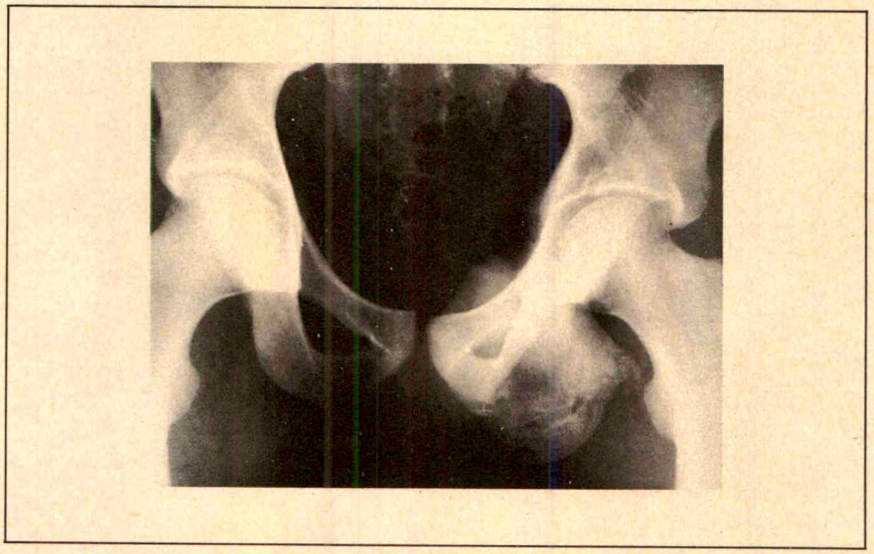

Figure 1.

From the Department of Radiology, Kaiser-Permanente Medical Center, Richmond, Calif.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr L. W. Young).

Denouement and Discussion

Traumatic Ischial Apophyseolysis

Fig 1.—Anteroposterior roentgenogram of pelvis. Large bony mass inferior to and replacing most of left ischial tuberosity is seen. Note radiolucent line of nonunion that, when present, is diagnostic of incompletely healed avulsion of ischial apophysis.

Fig 2.—Anteroposterior roentgenogram of pelvis made three years earlier shortly after acute injury shows moderate separation of crescent-shaped left ischial apophysis.

The roentgenographic appearance was pathognomonic for traumatic avulsion of the left ischial apophysis with subsequent exuberant callus reaction. Three years prior to the present injury, the patient was injured during basketball practice. At that time, he noted a sudden, severe pain in his left buttock. Roentgenograms showed a traumatic avulsion of the left ischial apophysis (Fig 2). The pain gradually subsided during the next several months. At the time of his second injury, the mass was palpable on careful examination but caused no discomfort despite its size. Slight functional disability, mainly an inability to fully flex his left knee, was noted. No treatment was undertaken.

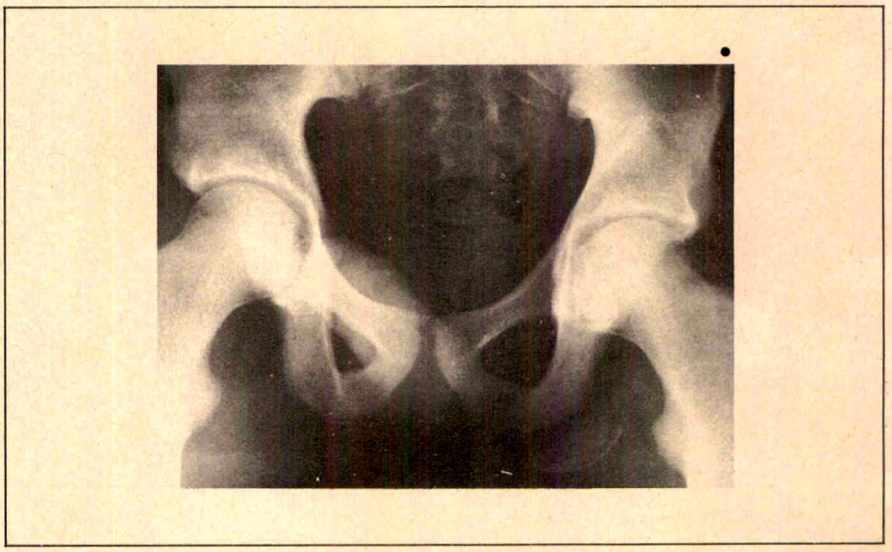

Figure 2.

Avulsion fracture of the ischial tuberosity is a rare but well-known clinical entity. This occurs typically between puberty and 25 years of age and relates to the time of appearance of the secondary ossification center and its fusion to the ischial tuberosity.[1] Avulsion results from sudden, vigorous pull of the hamstring muscle group and is found mainly in athletes, dancers, cheerleaders, and others engaged in similar activities.

The entity is of interest because the exuberant bony overgrowth following healing can cause it to be mistaken for a malignant neoplasm.[2,3] In two of previously reported cases, excision of the mass was performed because of the strong suspicion of malignant neoplasm.

Recognition of the lesion is, therefore, important. Radical surgical therapy such as amputation or hemipelvectomy can be avoided if a careful clinical history is obtained and the roentgenographic findings are carefully scrutinized. Often, previous roentgenograms showing the avulsed apophysis as a small crescentic rim of bone (Fig 2) are available for comparison. A characteristic follow-up finding is a well-delineated radiolucent line of nonunion that is usually found in two thirds of all cases.[3]

The differential diagnosis may include myositis ossificans, calcified hematoma, osteochondroma, enchondroma, or chondrosarcoma. Treatment is usually conservative, with no serious sequelae, though Schlonsky and Olix[4] have reported two cases that had persistent functional disability after conservative therapy. They recommend open reduction and fixation in cases in which the apophysis is widely separated.

Barnes and Hinds[3] found less than 40 cases of avulsion of the ischial apophysis reported in the English literature. In their analysis, they observed that 68% of the avulsions did not unite and that ten of the 14 cases treated surgically were late excisions of the mass mainly because of pain.

References

1. Ellis R, Green AG: Ischial apophyseolysis. *Radiology* 87:646-648, 1966.
2. Finby N, Begg C: Traumatic avulsion of ischial epiphysis simulating neoplasm. *N Y State J Med* 67:2488-2490, 1967.
3. Barnes S, Hinds R: Pseudotumor of the ischium: A late manisfestation of avulsion of the ischial epiphysis. *J Bone Joint Surg (Am)* 54:645-647, 1972.
4. Schlonsky J, Olix M: Functional disability following avulsion fracture of the ischial epiphysis. *J Bone Joint Surg (Am)* 54:641-644, 1972.

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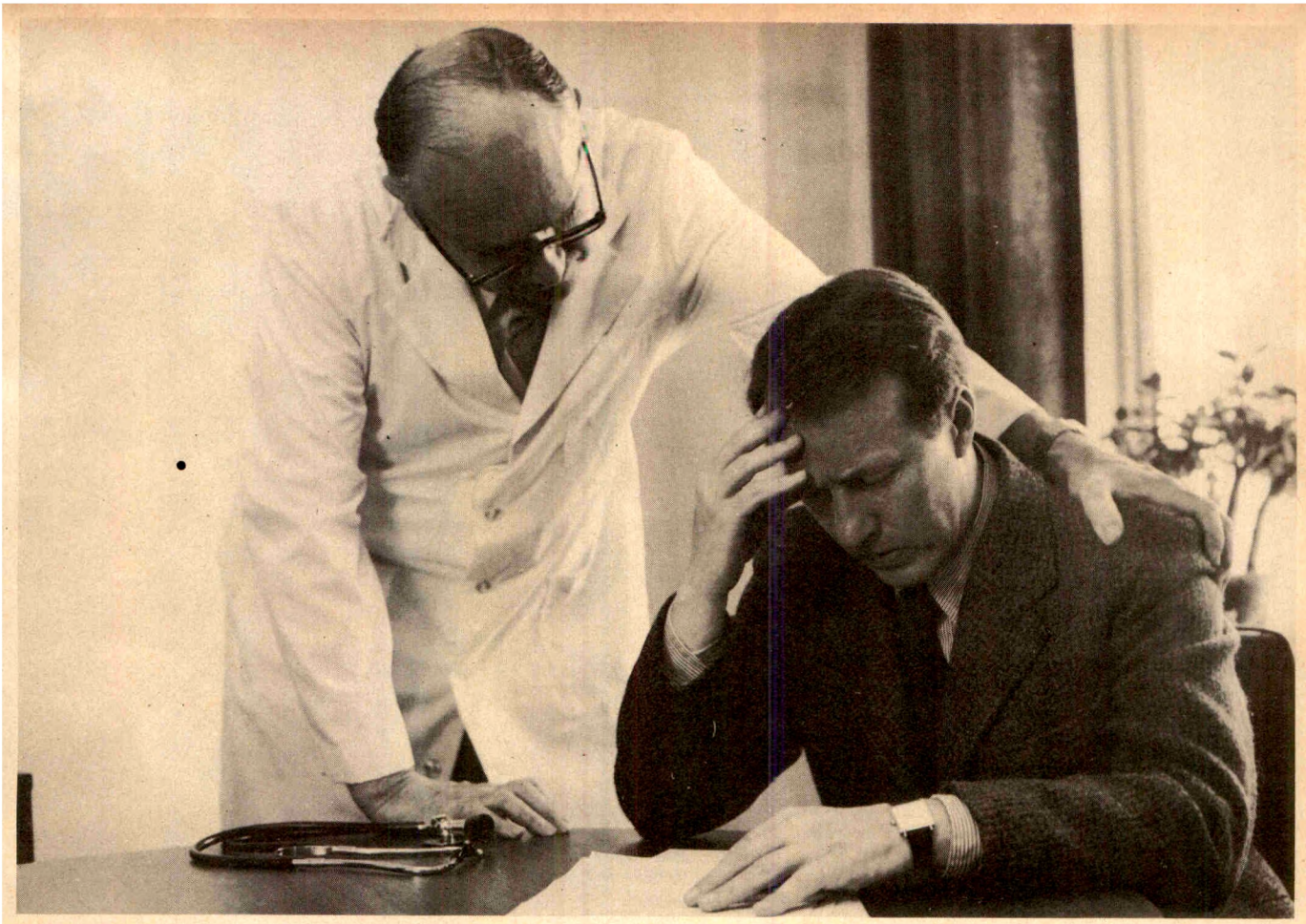

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HOW TO FIX

A FOUR-STEP BLUEPRINT

STEP 1.

INVITE 150 PRACTICING PHYSICIANS TO TALK ABOUT PEDIATRIC COUGH/COLD LIQUIDS.

THEN, LISTEN TO THEIR COMPLAINTS.

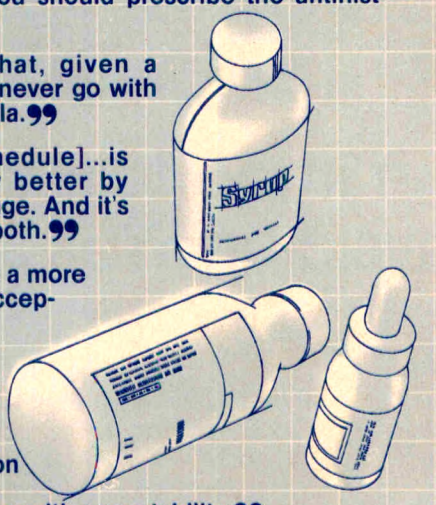
Sometimes a revolution begins by simply taking the obvious first step. Bristol Laboratories conducted a series of interviews and panel discussions with 150 physicians having active pediatric practices in all parts of the country.

Here are some of the comments heard most frequently:

"...they've had too many mixtures. If you want an antihistamine, you should prescribe the antihistamine plain."

"I've decided that, given a choice, I would never go with a narcotic formula."

"[A dosage schedule]...is really probably better by weight than by age. And it's helpful to have both."



"If you can, make a more concentrated, acceptable solution... higher doses of drug are more effective."

"...expectoration and decongestion are my prime objectives—along with acceptability."

"Pseudoephedrine is a stimulant. I don't think it's a good idea in infants under two years."

"[When treating very young children,] you don't want to suppress the cough."

"I do not prescribe codeine for small children. I prefer dextromethorphan."

"I think the taste factor is also important...so do the mothers!"

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STEP 2.

RECOGNIZE THAT WHAT *ISN'T* PUT PEDIATRIC COUGH/COLD LIQUIDS IS JUST AS IMPORTANT AS WHAT

Depending on patient age, these components regarded as undesirable by most of the physic consulted:

FOR INFANTS
No cough suppressant to interfere with expectoration of mucus.

FOR INFANTS & CHILDREN
No antihistamine to produce excessive drying side effects. Antihistamines are counterproductive to the mucous-liquifying action of expectorants.

FOR INFANTS & CHILDREN
No pseudoephedrine, with its assoc higher incidence of CNS side effects.

FOR INFANTS & CHILDR
No codeine or other narcotic d atives.

FOR INFANTS & CHILDREN
No subtherapeutic formulations, ri treatment failure or necessitating incre dosage.

INTRODUCIN

KIDS' COUGHS.
ATIONAL SYMPTOMATIC THERAPY.

STEP 3.

Y, DESIGN A SIMPLE, HIGH-POTENCY NFANT COUGH/COLD FORMULA.

(BEFORE PROCEEDING, REVIEW STEP 1.)

ch 1 ml dropperful contains:

enylpropanolamine HCl . . . . . 9 mg
aifenesin (glyceryl guaiacolate) . . . . . 30 mg
ohol 0.6%

r symptomatic relief of coughing and nasal d bronchial congestion due to colds, flu, bron- tis and croup.

e only major cough/cold formula in drops based) mg of expectorant action (guaifenesin) to en- ge productive coughing.

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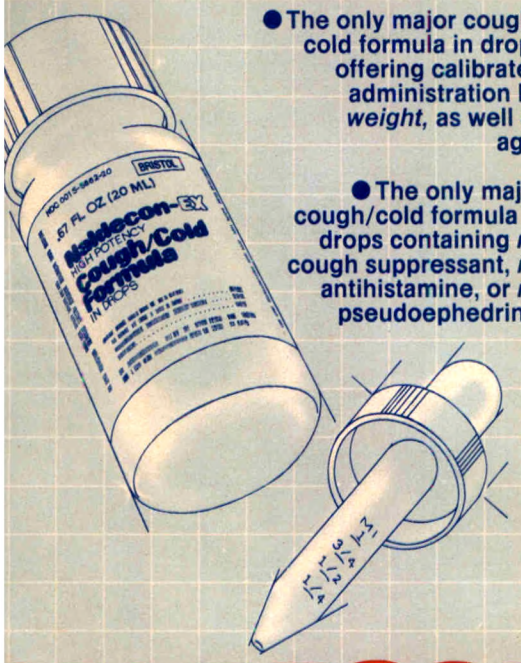


- The only major cough/cold formula in drops offering calibrated administration by *weight*, as well as age.
- The only major cough/cold formula in drops containing *no* cough suppressant, *no* antihistamine, or *no* pseudoephedrine!

STEP 4.

NEXT, DEVELOP A HIGH-POTENCY COUGH/COLD PRODUCT FOR AGES 2 TO 12.

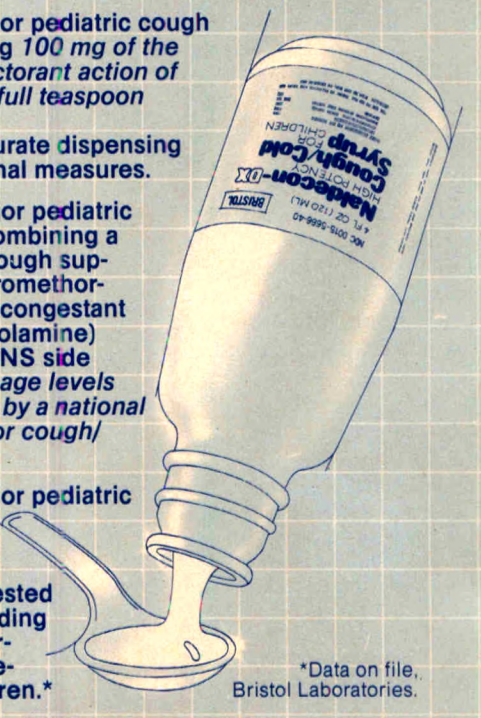
(REFER TO SPECIFICATIONS IN STEP 1.)

Each teaspoonful (5 ml) contains:

Phenylpropanolamine HCl . . . . . 9 mg
Dextromethorphan hydrobromide . . . . . 7.5 mg
Guaifenesin (glyceryl guaiacolate) . . . . . 100 mg
Alcohol 5%

For symptomatic relief of coughing and nasal and bronchial congestion due to colds or flu.

- The only major pediatric cough syrup delivering *100 mg of the powerful expectorant action of guaifenesin in full teaspoon doses.* —insuring accurate dispensing without fractional measures.
- The only major pediatric cough syrup combining a non-narcotic cough suppressant (dextromethorphan) and a decongestant (phenylpropanolamine) with minimal CNS side effects—*at dosage levels recommended by a national review panel for cough/cold products.*
- The only major pediatric cough syrup with the great Naldecon fruit flavor—taste-tested against the leading brand and overwhelmingly preferred by children.*



*Data on file, Bristol Laboratories.

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THE PRACTITIONERS' COUGH FIXERS

Clinical Memoranda

Unilateral Thyroid Enlargement With Hyperthyroidism

Single thyroid nodules are rare in childhood and adolescence. These nodules may be nonfunctioning, as is the case for the majority of benign adenomas,[1] or functioning. Functioning thyroid nodules may be nonautonomous[2] or autonomous. Data on the occurrence of autonomous thyroid nodules are scarce. Autonomous nodules function independently of the pituitary-thyroid axis; they do not respond to thyroid-stimulating hormone (TSH) nor are they suppressed by thyroxine therapy.[3] Such nodules have been reported in both euthyroid[4-7] and hyperthyroid individuals.[1,8-12] The term "toxic adenoma" describes only the latter group of patients.

The purpose of this report is to describe two girls who had hyperthyroidism and unilateral thyroid enlargement and in whom no other thyroid tissue could be palpated. The first patient had a toxic adenoma of the thyroid gland, whereas the second patient had Graves' disease with congenital absence of the contralateral lobe. The similar clinical presentation of these two patients illustrates difficulties that may be encountered in the evaluation of functioning thyroid nodules.

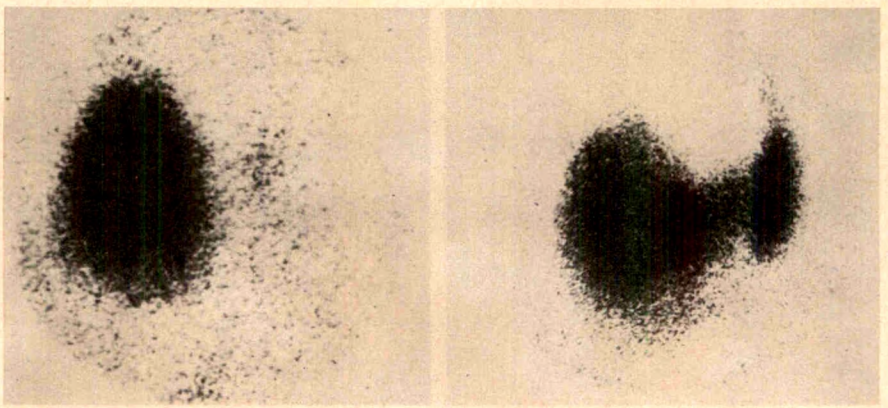
Report of Cases.—CASE 1.—A 6-year-old girl with a four-month history of hyperactivity, distractibility at school, heat intolerance, emotional lability, tremor, and restless sleeping was seen by her family pediatrician. There was no history of thyroid disease in the family. A smooth, firm, symmetrical, right-sided goiter was noted measuring 4 × 3 cm. The pulse rate was 130 beats per minute, blood pressure was 100/40 mm Hg, height was 129 cm (95th percentile), and weight was 22.5 kg (50th percentile). There was no exophthalmos or lid lag. The serum thyroxine (T_4) level was 17 μg/dL (normal, 5.6 to 12.6 μg/dL); serum TSH level was 2 μμ/mL (normal, < 10 μμ/mL); triiodothyronine (T_3) resin uptake was 42% (normal, 25% to 35%); uptake of ^{131}I at four hours was 23% (normal, 3% to 14%) and at 24 hours was 32% (normal, 6% to 29%). A technetium thyroid scan demonstrated a hot nodule in the right lobe (Fig 1) with no uptake in the left lobe. After propylthiouracil treatment (200 mg four times a day) for 2½ months, she was referred to us, at which time symptoms of hyperthyroidism had regressed and the serum T_4 level was 2.8 μg/dL and the serum TSH level was 50 μμ/mL. A repeated technetium thyroid scan was performed that again showed the nodule on the right but, in addition, considerable uptake in the left lobe (Fig 1). The patient had surgery and a 4 × 3-cm adenoma involving the right lobe of the thyroid was removed; the left lobe of the thyroid at time of surgery appeared normal. Subsequent to surgery, and without receiving medication, she is clinically and biochemically euthyroid.

CASE 2.—A 5-year-old girl had a six-month history of fidgetiness, tremor, increased frequency of bowel movements, insomnia, and accelerated linear growth. There was no family history of thyroid disease. On physical examination, exophthalmos and lid lag were present. There was a smooth, firm, symmetrical left-sided goiter measuring 2.5 × 3 cm; thyroid tissue could not be palpated on the right side of the neck. There was no bruit over the goiter. In addition, a gross tremor of the fingers and hands was noted, the palms were moist, the pulse rate was 130 beats per minute, blood pressure was 110/50 mm Hg, a grade 2/6 ejection systolic murmur was present along the left sternal border, the height was 122 cm (2 cm above the 97th percentile), and weight was 17.5 kg (40th percentile). The serum T_4 level was 16 μg/dL, T_3 resin uptake was 42%, and serum TSH level was less than 2 μμ/mL. Uptake of ^{131}I was 48% at two hours and 73% at 24 hours. A technetium TC 99m thyroid scan showed uniform increased uptake on the left but no uptake on the right (Fig 2). After propylthiouracil therapy (5 mg/kg/24 hr in three divided doses), the patient became euthyroid but subsequently fever, rash, arthritis, and leukopenia developed that necessitated discontinuation of drug therapy. When the drug therapy was discontinued, the patient had an exacerbation of hyperthyroidism that was then successfully treated with radioactive sodium iodide I 131; a total of 18 mCi of radioactive iodine was given in three doses during a 15-month period. (A TSH stimulation test performed when the patient was euthyroid was discontinued after one injection of bovine TSH, 5 IU, because of untoward side effects.) At present, she is clinically and biochemically euthyroid (serum TSH, 5 μμ/mL; T_4, 6.9 μg/dL) without therapy one year after her last radioactive iodine treatment.

Comment.—In 1956, Hayles and associates[1] described the first case of childhood toxic adenoma in a 7-year-old girl. The diagnosis was confirmed histologically. Since then, ten cases of autonomous single thyroid nodules in children have been reported. Five of these occurred in euthyroid patients[4-7]; the remaining five[8-12] as well as the patient described by Hayles et al[1] had associated hyperthyroidism. Molnar et al[13] suggested that clinical toxicity does not appear until the nodule is at least 3 cm in diameter. However, patients with large autonomous nodules may remain euthyroid.[14] All patients with toxic adenoma had biochemical evidence of hyperthyroidism; three had elevated T_3 levels[8,9,11] and Popma et al[8] suggest that T_3 may be preferentially secreted by toxic adenomata. Although the demonstration of function in a nodule largely excludes a malignant diagnosis,[15] thyroid carcinoma causing hyperthyroidism has been described.[16]

It is difficult to clinically differentiate toxic adenoma from Graves' disease involving one lobe of the thyroid gland with congenital absence of the contralateral lobe. In general, patients with toxic adenoma have milder and fewer toxic symptoms than do pa-

Fig 1.—Thyroid scan of case 1 before (left) and after (right) propylthiouracil treatment. Note uptake in both lobes after propylthiouracil reflecting thyroid-stimulating hormone effect (case 1).



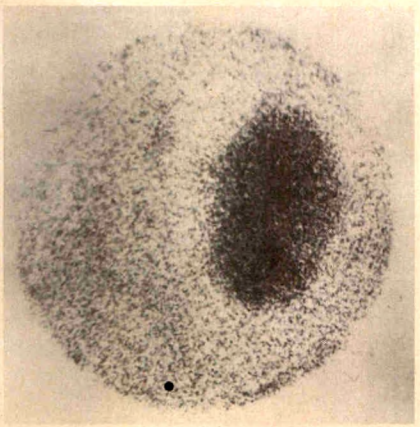


Fig 2.—Thyroid scan of case 2 showing diffuse increased uptake of radioisotope on left side with absence of uptake on right side (case 2).

tients with Graves' disease. Plummer emphasized lack of ocular changes as the most important clinical feature differentiating toxic adenoma from Graves' disease in adults.[7] Having reviewed the childhood cases of toxic adenoma, we believe that the same phenomenon is true in children. The presence of exophthalmos and lid lag in our second patient suggested the diagnosis of Graves' disease. The diagnosis was established by thyroid scan that showed generalized thyroid enlargement on the left side and absence of any thyroid tissue on the right. When the diagnosis of Graves' disease with congenital absence of one lobe is in doubt, one can determine serum levels of thyroid-stimulating immunoglobulin[17] and perform a TSH stimulation test followed by a ^{99m}Tc thyroid scan.[10] Results of the former test will usually be positive in Graves' disease and the latter test will show absence of any thyroid tissue on the contralateral side after TSH stimulation.

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Joyce Cunningham provided assistance in the preparation of this manuscript.

Nonproprietary Name and Trademarks of Drug

Sodium iodide I 131—*Iodotope I-131, Oriodide-131, Theriodide-131.*

1. Hayles AB, Kennedy RLJ, Woolner LB, et al: Nodular lesions of the thyroid gland in children. *J Clin Endocrinol Metabol* 16:1580-1594, 1956.
2. Rosenbloom AL: Functioning solitary nodule of the thyroid in a child. *J Pediatr* 82:491-494, 1973.
3. Burman KD: Solitary autonomous thyroid nodule. *Postgrad Med* 56:70-74, 1974.
4. Rosenbloom AL, Moore MM: Hyperfunctioning adenoma in a euthyroid adolescent. *South Med J* 66:1247-1249, 1973.
5. Rosenbloom AL, Pierson KK: Nodule toxic goitre (Plummer's disease) in a child. *J Pediatr* 84:104-107, 1974.
6. Hahn HB: Autonomous thyroid nodules in children. *Tex Med* 68:102-105, 1972.
7. Zabransky S, Koppenhagen K, Waldschmidt J: Autonomous adenoma of the thyroid in infancy. *Z Kinderheilkd* 120:51-57, 1975.
8. Popma BH, Cloutier MD, Hayles AB: Thyroid nodule producing T3 toxicosis in a child. *Mayo Clin Proc* 48:273-275, 1973.
9. Taylor HC: Solitary hyperfunctioning thyroid adenoma in a child: Elevated T_3 and T, levels with normal TSH level. *JAMA* 234:1253-1255, 1975.
10. Hopwood NJ, Carroll RG, Kenny FM, et al: Functioning thyroid masses in childhood and adolescence: Clinical, surgical and pathologic correlations. *J Pediatr* 89:710-718, 1976.
11. Granoff AB, Hershman JM: Suppression of pituitary TSH in a child with a hyperfunctioning thyroid nodule. *J Pediatr* 90:83-85, 1977.
12. Serafimov N, Dolgova-Kerubin V, Doneva V: Autonomous functioning thyroid adenoma in a 6-year boy. *Acta Med Iugosl* 32:181-184, 1978.
13. Molnar GD, Wilber RD, Lee RE, et al: On the hyperfunctioning nodule. *Mayo Clin Proc* 40:665-684, 1965.
14. Silverstein GE, Burke G, Cogen R: The natural history of the autonomous hyperfunctioning thyroid nodule. *Ann Intern Med* 67:539-548, 1967.
15. Fisher DA: Thyroid nodules in childhood and their management. *J Pediatr* 88:866-868, 1976.
16. Sussman L, Librik L, Clayton TW: Hyperthyroidism attributable to a hyperfunctioning thyroid carcinoma. *J Pediatr* 72:208-213, 1968.
17. Volpe R: The pathogenesis of Grave's disease. *Clin Endocrinol Metabol* 7:3-29, 1979.

Hydrops of the Gallbladder

Hydrops of the gallbladder is an uncommon problem in infants and children. Most cases of hydrops of the gallbladder previously reported are seen as a complication of other illnesses, such as upper respiratory tract infections, salmonellosis, cervical adenitis, and pseudomonas sepsis in children with severe burns and diarrhea. Hydrops has also been associated with systemic infections caused by leptospirosis and group A streptococcal infection as scarlet fever.[1-3] We report a neonate with group B streptococcal sepsis and pneumonia in whom gallbladder hydrops developed that completely resolved without further complications after seven days of antibiotic therapy.

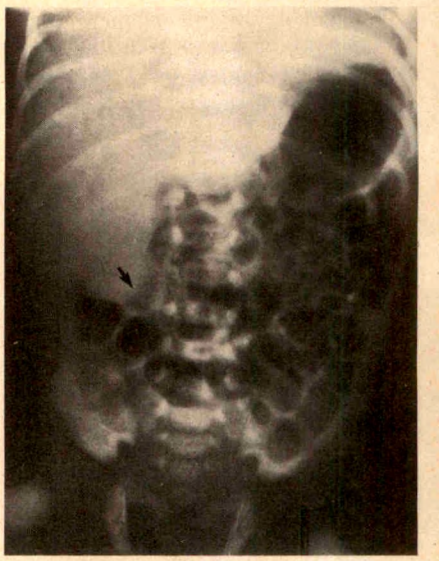


Fig 1.—Plain film of abdomen showing soft-tissue mass density (arrow) extending caudad from liver edge in right upper abdominal quadrant.

Report of a Case.—The patient is a 3,240-g, term male infant born to a 34-year-old mother after an uncomplicated pregnancy and delivery. At 8 hours of age, progressive respiratory distress, fever to 40 °C, and hypotension developed. Roentgenograms of the chest demonstrated diffuse infiltrates in both lung fields. Respiratory decompensation, shock, and acidosis were managed with assisted ventilation, transfusion of whole blood, bicarbonate, and intravenous (IV) dopamine infusion. Cultures were obtained and IV ampicillin sodium and gentamicin sulfate therapy were started.

By the third day of life, when the initial respiratory distress and shock were resolving, a palpable mass was noted in the right upper quadrant of the abdomen, as well as a well-defined roentgenographic density in the same location (Fig 1). Abdominal distension and generalized edema also developed at this time. Real-time ultrasonography of the abdomen, using a 7.4-mHz linear array system, demonstrated a dilated gallbladder without evidence of calculi or intrahepatic biliary obstruction (Fig 2). Necrotizing enterocolitis was also suspected and oral feeding was discontinued. Intermittent nasogastric suction was started and the abdominal distension resolved within 24 hours.

Cultures of the blood, gastric aspirate, and external ear canal obtained at admission grew group B β-hemolytic streptococcus. A second abdominal ultrasound study four days after the initial study showed resolution of the hydrops (Fig 3). Intravenous antibiotic therapy was continued for two weeks and the baby was discharged in good condition at 3 weeks of age.

Comment.—Acute distension of the

gallbladder is very uncommon during the neonatal period. Among the cases in infants reported by Bloom and Swain,[2] anatomic obstruction to the cystic duct was the usual predisposing factor. Two cases of acute cholecystitis due to *Str viridans*[4] and *Escherichia coli*[5] have been reported in infants less than 3 weeks old. Robinson et al[6] described three cases of hydrops of the gallbladder in neonates due to group B β-hemolytic streptococcus, *Serratia marcescens*, and α-streptococcus. Surgery was performed on all three.

However, spontaneously resolving hydrops of the gallbladder in the neonatal period has not been described.

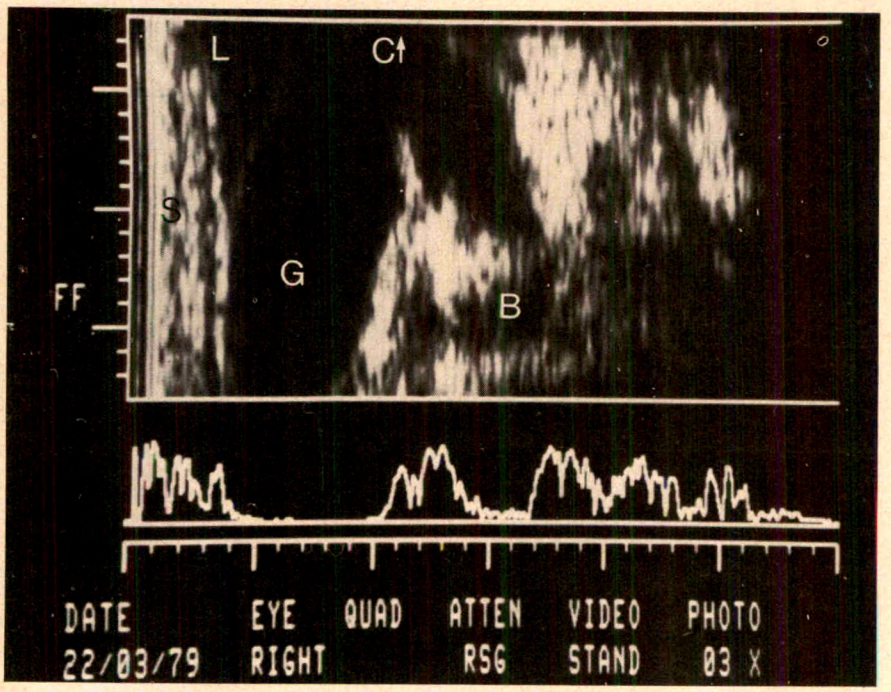
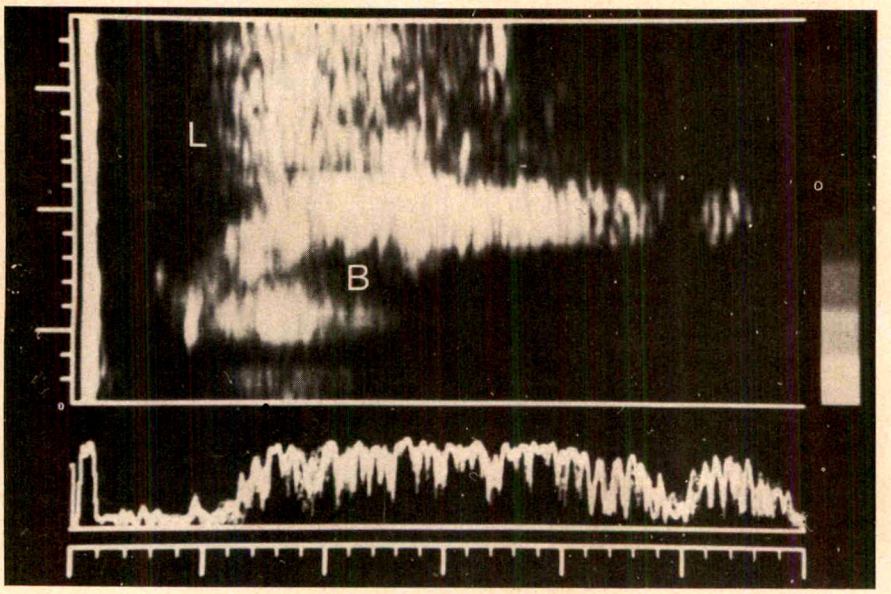


Fig 2.—Sagittal abdominal scan, 3 cm to right of midline demonstrates inferior margin of right lobe of liver (L), dilated gallbladder (G), and bowel (B): abdominal wall (S) and cephalad (C↑).

Fig 3.—Sagittal abdominal scan performed in same projection, four days later, showing only right lobe of liver (L) and bowel (B).



Our patient with group B streptococcal sepsis is of interest since the association of acute gallbladder dilation with scarlet fever is well documented.[3] The pathogenesis of the hydrops associated with group A streptococcal infection is not certain. Among cases undergoing surgical drainage, isolation of the organism from bile is uncommon.[3] Hyperplasia of the lymph nodes adjacent to the junction of the cystic and common bile duct has been described in some cases.[7,8] The possibility of transient edema of the biliary ducts related to streptococcal sepsis has also been suggested.[2,9] The hydrops in our patient was associated with generalized edema and abdominal distention.

Several reports of hydrops of the gallbladder in older children have recommended treatment with cholecystectomy or cholecystotomy.[1-3,9] Ultrasonography, as previously reported by Kumari et al[10] is a valuable noninvasive tool to diagnose hydrops. By sequential ultrasound studies, the resolution of the dilation can be monitored and surgical intervention avoided in a critically ill patient.

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Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S, Polycillin-N, Principen/N.*

Gentamicin sulfate—*Garamycin.*

1. Ternberg LJ, Keating JP: Acute acalculous cholecystitis as a complication of other illnesses in childhood. *Arch Surg* 110:543-547, 1975.

2. Bloom RA, Swain VA: Non-calculus distension of the gallbladder in childhood. *Arch Dis Child* 41:503-508, 1966.

3. Strauss GR: Scarlet fever with hydrops of the gallbladder. *Pediatrics* 44:741-745, 1969.

4. Pieretti R, Auldist AW, Strephens CA:

Acute cholecystitis in children. *Surg Gynecol Obstet* 140:16-18, 1975.

5. Crystal RW, Fink RL: Acute acalculous cholecystitis in childhood. *Clin Pediatr* 10:423-426, 1971.

6. Robinson AE, et al: Cholecystitis and hydrops of the gallbladder in the newborn. *Radiology* 122:749-751, 1977.

7. Rankin W: Acute distension of the gallbladder in children. *Arch Dis Child* 30:60-61, 1955.

8. Lee CM Jr, Englender GS: Massive hydrops of the gallbladder producing pyloric obstruction in a 7-year-old boy. *Pediatr* 11:449-453, 1953.

9. Chamberlain JW, Hight DW: Acute hydrops of the gallbladder in childhood. *Surgery* 68:899-905, 1970.

10. Kumari S, Lee WJ, Baron MG: Hydrops of the gallbladder in a child: Diagnosis by ultrasonography. *Pediatr* 63:295-297, 1979.

Apparent Protein-Losing Enteropathy Associated With Giardiasis

Giardia lamblia is a flagellated protozoan that frequently inhabits the human proximal small intestine and is pathogenic on occasion.[1,2] When it is pathogenic, mucosal injury may be minimal to severe, and frequently is patchy in distribution.[1-3] Diarrhea, steatorrhea, nausea, anorexia, and epigastric fullness have been well established, but association with a protein-losing enteropathy has not been appreciated.[1-4] We studied a 5-year-old boy with giardiasis and apparent protein-losing enteropathy that subsequently resolved after treatment of giardiasis with metronidazole.

Report of a Case.—A 5-year-old boy was admitted to the University of California Medical Center, San Francisco, with a two-day history of swelling in his legs and around his eyes, as well as abdominal protuberance. Six days prior to admission, the patient had begun to vomit, but there was no fever, diarrhea, or other symptoms. Medical history and results of a systems' review were unremarkable. One month prior to admission, the patient had visited a campground and drunk well water there. Results of physical examination were unremarkable except for mild periorbital, pretibial, and pedal edema without abdominal distention.

Results of laboratory studies included the following values: hemoglobin, 12.9 g/dL; hematocrit, 38%; and WBC count, 7,300/cu mm, with normal differential count and normal numbers of platelets and eosinophils. There were normal sedimentation rates, serum transaminase levels, creatinine levels, electrolyte levels, ammonia levels, folate levels, and vitamin B_{12} levels. Results of urinalysis and sweat tests were normal. Calcium level was 7.6 mg/dL; phosphorus level, 3.7 mg/dL; total protein level, 2.8 g/dL; albumin level, 2.2 g/dL; IgG level, 175 mg/dL (normal, > 500 mg/dL); IgM level, 77 mg/dL (normal, > 40 mg/dL); IgA level, 89 mg/dL (normal, > 55 mg/dL); IgE level, 31 units/mL (normal, < 100 units/mL); and prothrombin time, 13.5 s (control, 11.0 s). Stool examinations were negative for occult blood and reducing substances, and culture was negative for pathogens but did demonstrate *G lamblia* cysts. Quantitative stool fat collection (72 hours) was normal (< 7%). ^{51}Cr-labeled albumin was not available. Upper gastrointestinal-small bowel roentgenograms demonstrated mild thickening of the mucosal contour of the mid- and distal duodenum, as well as the jejunum. A small-intestinal biopsy specimen is shown in the Figure.

After apparent intolerance to quinacrine hydrochloride (Atabrine), treatment with metronidazole (Flagyl) for ten days resulted in a disappearance of the peripheral edema and normalization of all laboratory values; levels of serum protein rose to 6.3 g/dL, and of albumin to 4.1 g/dL. Repeated examinations for parasites were negative. The patient has continued to do well clinically at a follow-up examination three months later.

Comment.—As previously mentioned, *G lamblia* is a protozoan agent

Specimen of distal duodenum. Epithelium is columnar and intact. Villi are tall and leaf-like. Lymphocytes, plasma cells, and occasional eosinophils are present in lamina propria. Flagellated structures (arrowheads and inset) are present adjacent to and in apposition to epithelial surface (hematoxylin-eosin, ×125; inset, ×250).

that may infest the proximal small intestine, specifically the duodenum and jejunum. Mucosal damage may result.[1-5] The infestation occurs by ingestion of cysts of *G lamblia*, the source being feces of an infected person or water and food contaminated with contaminated feces.[1-5] The prevalence in the United States has been estimated as 7% to 8%.[1-5]

Clinically, most children are asymptomatic. Others may have an acute onset of nausea, diarrhea (watery), decreased appetite, with or without crampy abdominal pain, frequently self-limited in course.[1,2,6] Still others may have an intermittent or chronic course, characterized by diarrhea, sometimes steatorrhea, and variable failure to thrive.[1,2,5] Secondary disaccharide intolerance, particularly lactose, may be a prominent feature. There is a higher incidence of giardiasis in children with immunodeficiency states, eg, acquired hypogammaglobulinemia.[3,5] Protein-losing enteropathy has not been appreciated in giardiasis, especially without diarrhea, as in our patient. The possible mechanisms in our patient remain unknown, although mechanical blockade of the mucosa by the parasite, submicroscopic changes in the mucosa, as suggested by other investigators in explaining malabsorption in giardiasis, may play a role.[7,8] The resolution of these features coincided with successful treatment with metronidazole, since quinacrine had not been tolerated. Repeated examinations for parasites were negative, and clinical status and laboratory study results became normal. Thus, our patient represents an apparent protein-losing enteropathy associated with intestinal giardiasis.

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Larry McDonald, MD, referred the patient, and Barbara Jarvis assisted in preparation of the manuscript.

Nonproprietary Name and Trademark of Drug

Metronidazole—*Flagyl*.

1. Ament ME: Diagnosis and treatment of giardiasis. *J Pediatr* 80:633-637, 1972.
2. Barbieri D, de Brito T, Hoshino S, et al: Giardiasis in childhood. *Arch Dis Child* 45:466-472, 1970.
3. Ament ME, Rubin CE: Relation of giardiasis to abnormal immunodeficiency syndrome. *Gastroenterology* 62:216-226, 1972.
4. Hoskins LC, Winawer SJ, Broitmans A, et al: Clinical giardiasis and intestinal malabsorption. *Gastroenterology* 53:265-279, 1967.
5. Wolfe MS: Giardiasis. *JAMA* 233:1362-1365, 1975.
6. Waldmann TA: Protein-losing enteropathy. *Gastroenterology* 50:422-443, 1966.
7. Barbieri D, de Brito T, Hoshino S, et al: Giardiasis in childhood: Absorption tests and biochemistry, histochemistry, light, and electron microscopy of jejunal mucosa. *Arch Dis Child* 45:466-472, 1970.
8. Hoskins LC, Winawer SJ, Broitman SA, et al: Clinical giardiasis and intestinal malabsorption. *Gastroenterology* 53:265-279, 1967.

Fatal Group G Streptococcal Sepsis in a Preterm Neonate

The etiology of neonatal infections has undergone certain changes, with an important consideration being the emergence of the group B streptococcus as a major pathogen in the newly born. A number of non-group B streptococci have been shown to cause infections clinically simulating group B streptococcal infection, namely, A, C,[1] D,[2] and more recently, G.[3-6] We report a fatal case of group G streptococcal septicemia in a 2-kg preterm infant.

Report of a Case.—Twin males were born to a 27-year-old, gravida 2, para 1, white woman by spontaneous vaginal delivery at 32 weeks' gestation. The pregnancy had been uncomplicated, and artificial rupture of membranes three hours prior to delivery yielded clear amniotic fluid. Each had Apgar scores of 5 and 6 at 1 and 5 minutes of age. Initial examination revealed the lengths and head circumference to be in the 50th percentile for the gestational age and the weights to be in the 50th and 75th percentiles, respectively. No congenital malformations were identified. Both infants experienced the early onset of respiratory distress. An umbilical arterial catheter was inserted in twin B and blood was obtained for culture. Both infants were intubated and ventilated because of the finding of increased partial pressure of carbon dioxide and were transferred to the regional neonatal intensive care unit at 3 hours of age.

Physical examination at this time revealed active, pink infants with good peripheral pulses and perfusion. The lung fields were clear on auscultation. A Gram-stained sample of the gastric aspirate from twin B revealed fewer than 5 polymorphonuclear leukocytes per high-power field and no organisms. The WBC count was 11,700/cu mm, with 46% polymorphonuclear leukocytes, 2% band forms, 37% lymphocytes, and 15% monocytes. A chest roentgenogram was consistent with the presence of hyaline membrane disease. By 14 hours of age, twin B had been weaned to a continuous positive airways pressure of 4 mm Hg and oxygen concentration of 27%, but at 20 hours of age, progressive hypoxemia and acidosis developed, which could not be reversed by sustained ventilatory assistance and infusions of sodium bicarbonate and tromethamine (Tham). Samples of blood and spinal fluid were obtained for culture. The Gram-stained specimen of the tracheal aspirate showed rare polymorphonuclear leukocytes, 0 to 3 squamous epithelial cells per high-power oil immersion field, and large numbers of Gram-positive cocci in chains. The blood showed marked neutropenia (total WBC count, 3,500/cu mm, with 8% polymorphonuclear leukocytes). A chest roentgenogram suggested bilateral pulmonary infiltrates. Antibiotics (penicillin G sodium and gentamicin sulfate) were given in appropriate doses. Clinical deterioration continued, with progressive hypoxemia, acidosis, hypotension, renal failure, hyperkalemia, and cardiac arrhythmias, and death occurred at 44 hours of age.

Autopsy performed on twin B demonstrated pneumonic consolidation of both lung fields and the presence of bilateral intraventricular hemorrhages. Microscopic examination of the lung showed diffuse intra-alveolar fibrin deposition, with scattered RBCs, polymorphonuclear leukocytes, and macrophages. Eosinophilic hyaline membranes were seen throughout. On microscopic examination, the brain showed hemorrhagic congestion of the choroid with packed RBCs and fibrin in the ventricles.

Twin A showed improvement with ventilatory support and was extubated at 30 hours of age and placed in 30% oxygen. In view of twin B's deteriorated condition from presumed sepsis, samples were obtained from twin A for culture and the infant was treated with penicillin for ten days.

Cultures of gastric and tracheal aspirates, nose, axilla, CSF, and blood from twin B were studied. Blood cultures were processed radiometrically by the use of Bactec (Johnson Laboratories, Cockey's Ville, Md). Three sets of blood were drawn for aerobic and anaerobic culture study, two sets on two successive days (at 2 and 30 hours of age) and one set post mortem. The blood sample taken at 30 hours of age was positive, after 24 hours incubation, for a β-hemolytic streptococcus. This organism was presumptively identified as Lancefield group G by the coagglutination method of Kronvall[7] and confirmed by the Laboratory Division of the Connecticut State Department of Health, Hartford, using Lancefield's precipitin method. The sample of tracheal aspirate obtained at 28 hours of age also yielded group G streptococcus. Cultures from the axilla, nose, and gastric aspirate, as well as the first and third set of blood cultures and culture of the CSF, were sterile. Similar cultures from the other

twin were uniformly negative.

Bacteriologic survey of the transport van, intensive care unit, and the incubator failed to disclose the presence of group G streptococcus. The mother of the twins remained asymptomatic at another hospital; vaginal culture was not performed.

Comment.—With the development of group B β-hemolytic streptococcus as a major pathogen in the neonatal period, other streptococci of Lancefield's classification have come under scrutiny. Group A, group C,[1] group D,[2] and group G[3-6] streptococci have been reported as probable causes of neonatal infections.

Group G streptococcal infections in humans have been reported since the late 1930s.[8] Group G streptococci have been isolated from a variety of human sources, including suppurative wounds, blood, urine, vaginal secretions, CSF, feces, and other body fluids.[9] The most frequently reported sources have been wounds,[9] the respiratory tract,[10,11] and the genital tract.[2,12]

Christensen et al[13] examined the frequency of isolation of β-hemolytic streptococci from urethral and cervical swabs in 364 female patients who were being studied for gonococcal infection and found the frequency of urogenital colonization by group G streptococcus to be 0.5%. In only rare instances, however, has neonatal sepsis been reported. Baker[3] and Ancona et al[6] cited instances in which group G streptococci were isolated from both the blood of the infant and the vagina of the mother; the mothers had prolonged rupture of membranes. There was a striking clinical similarity to "early onset" group B streptococcal infection, as noted in the present report. Brans[4] reported septicemia in two neonates. These cases differ in that in both instances, group B streptococci were isolated concomitantly with group G streptococci, although not necessarily from the same site. The author did not specify the methods used to differentiate the streptococci, but it is known that serologic cross reactions do exist between group B and group G streptococci.[14] Thus, one must question, on the basis of these dual isolates, the presence of group G streptococcus, and if so, its role in the disease process.

In our case, group B streptococci were not isolated from either twin. The streptococci were identified serologically by coagglutination with specific antisera. On 10% sheep blood agar plates, the colonies produced β-hemolysis but were tiny (< 1 mm in diameter). Colony morphology is variable and hence cannot be easily differentiated from colonies of group B streptococci that are larger (> 2 mm), gray, and often mucoid.

Nieburg[5] reported group G streptococcal sepsis in a full-term infant following an uncomplicated pregnancy, labor, and delivery. The clinical course was similar to that of our infant (absence of risk factors, progressive respiratory deterioration, shock, and coagulopathy) and ended fatally. Two out of three antemortem blood cultures yielded group G streptococcus. The fetal scalp electrode used in intrapartum fetal monitoring was implicated as effecting a possible port of entry for the organism. The fact that in our case, invasive procedures such as intubation and umbilical vessel catheterization were performed during transfer to the regional center, with subsequent positive cultures, raises the issue of nosocomial infection. Examination of our transport and nursery incubators and equipment revealed no evidence of contamination. Hence, it is likely that under the circumstances described, the infant was infected during parturition.

Reports of neonatal infections caused by streptococci of different serologic groups underscore the need for the precise identification of streptococcal isolates through the use of group specific antisera.

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Nonproprietary Name and Trademark of Drug

Gentamicin sulfate—*Garamycin.*

1. Stewardson-Krieger P, Gotoff SP: Neonatal meningitis due to group C beta hemolytic streptococcus. *J Pediatrics* 90:103-104, 1977.

2. Duma RJ, Weinberg AN, Medrek EF, et al: Streptococcal infections: A bacteriologic and clinical study of streptococcal bacteremia. *Medicine* 48:87-127, 1969.

3. Baker CJ: Unusual occurrence of neonatal septicemia due to group G streptococcus. *Pediatrics* 53:568-570, 1974.

4. Brans YW: Group G streptococcal sepsis. *Pediatrics* 55:745-746, 1975.

5. Nieburg PI: Fatal group G streptococcal sepsis in a neonate. *Scand J Infect Dis* 11:93-95, 1979.

6. Ancona R, Thompson TR, Ferrieri P: Group G streptococcal pneumonia and sepsis in a newborn infant. *J Clin Microbiol* 10:758-759, 1979.

7. Kronvall G: A rapid slide agglutination method for typing pneumococci by means of specific antibody absorbed to protein A containing staphylococci. *J Med Microbiol* 6:187-190, 1973.

8. Macdonald I: Fatal and severe human infections with hemolytic streptococci group G (Lancefield). *Med J Aust* 2:471-474, 1939.

9. Cunniff H, Bump CM: Extrarespiratory non-group A, non-group D isolates of streptococci. *Am J Med Tech* 42:195-200, 1976.

10. Nordlander IM, Thal E, Tunevall G: Occurrence and significance of hemolytic streptococci groups B-U in human infectious disease. *Scand J Infect Dis* 7:35-38, 1975.

11. Hill HR, Caldwell GG, Wilson E, et al: Epidemic of pharyngitis due to streptococci of Lancefield group G. *Lancet* 2:371-374, 1969.

12. Hill AM, Butler AM: Hemolytic streptococcal infections following childbirth and abortion. *Med J Aust* 1:293-299, 1940.

13. Christensen KK, Christensen P, Flamholc L, et al: Frequencies of streptococci of groups A, B, C, D and G in urethra and cervix swab specimens from patients with suspected gonococcal infection. *Acta Pathol Microbiol Scand* 82B:470-474, 1974.

14. Curtis SN, Krause RM: Antigenic relationships between groups B and G streptococci. *J Exp Med* 120:629-637, 1964.

TAR Syndrome: Dorsal Pedal Edema and Excessive Perspiration

The thrombocytopenia absent radius (TAR) syndrome is inherited in an autosomal-recessive manner and consists of thrombocytopenia during the neonatal period, a leukemoid reaction during the first year of life, eosinophilia, anemia, bilateral absence of the radius, radial deviation of the hand, abnormalities of the ulna and humerus, other skeletal anomalies, micrognathia, and congenital heart disease. Bleeding, specifically intracranial bleeding, is potentially the most serious problem.

Report of Cases.—We recently evaluated this syndrome in eight patients and noted two findings that have not been, to our knowledge, previously reported in association with this syndrome: dorsal edema of the feet and excessive perspiration. Two of the patients were brothers and two were first cousins. Six of the eight patients had nonpitting edema of the dorsa of their feet at birth. The duration of the edema varied. In one infant, it was no longer present at 3 months and in another it had disappeared by 18 months. It continues to be present in a 1-month-old, a 5-month-old, and two 15-month-old children. The cause of the edema is not known, although it may represent an abnormality of the lymphatic system. Some of the patients also had redundancy of the skin of the neck.

Excessive perspiration occurred in seven of the eight patients and is still present in all of the patients, the oldest being 21 months. This may be secondary to vasomotor instability or an increased metabolic rate.

Comment.—We have noted that some patients with missing limbs also have increased perspiration that may be related to decreased body surface. We conclude that dorsal edema of the feet and excessive perspiration are frequent findings of the TAR syndrome.

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1. Hall JG, Levin J, Kuhn JP, et al: Thrombocytopenia with absent radius. *Medicine* 48:411-439, 1969.

Tracheoesophageal Fistula in Parent and Offspring: A Rare Occurrence

Infants born with esophageal atresia and tracheoesophageal fistula (TEF) had a grim prognosis prior to the 1940s. However, with better anesthesia, better operative management (delayed, staged, or primary), and neonatal intensive care units, the survival of patients with this anomaly has increased to 75% to 90%. The patients who survived in the 1940s and 1950s are now producing children who may have an increased likelihood of esophageal anomalies.

This report details the occurrence of esophageal atresia with a distal fistula in the father and an H-type tracheoesophageal fistula in his daughter.

Report of Cases.—CASE 1.—A 2.9-kg baby boy born at term in 1955 vomited all feedings and had heavy oral secretions noted after a normal delivery at an outlying hospital. Diagnosis of esophageal atresia was made on the fourth day of life and a gastrostomy was performed with the patient under local anesthesia. The infant was fed through the gastrostomy for seven days. (This is not desirable because of the risk of pulmonary aspiration through the tracheoesophageal fistula. Division of the fistula and gastrostomy or intravenous hyperalimentation is preferable, if the condition of the infant precludes immediate repair of the esophageal atresia). At 12 days of age, the infant was transferred to Children's Hospital of Pittsburgh. A transpleural division of the tracheoesophageal fistula and a primary esophageal anastomosis was performed. The child did well and was discharged on the 13th postoperative day. Twenty-two years later, his daughter was admitted to Children's Hospital of Pittsburgh with recurrent pneumonia.

CASE 2.—A 6-month-old girl had been hospitalized elsewhere for pneumonia at 3 and 5 months of age. The referral to Children's Hospital of Pittsburgh was made for "problems with swallowing liquids" and "aspiration pneumonia." As an infant, she would refuse liquids in favor of solid baby foods or formula thickened with cereal. The parents noted coughing and choking when liquids were taken. The diagnosis of an H-type TEF was established by barium swallow. At endoscopy, the fistula was easily visualized at the level of the sixth cervical vertebra. The child weighed 4.1 kg and seemed healthy, except for occasional cough when liquids were swallowed. At operation, a ureteral catheter was passed endoscopically from the trachea into the esophagus. The fistula was approached through a right cervical incision. Identification and division of the fistula was easily accomplished, and the child went home in eight days, eating liquids and solids without any symptoms. She has been seen in follow-up examinations for more than a year and is perfectly well. She has a normal esophagram.

Comment.—Esophageal atresia occurs approximately once in every 4,000 live births.[1] The error in development is thought to occur during the third or fourth week of fetal life.[2] While the empirical chance of a single malformation recurring in immediate relatives is said to be 3% to 5%, this does not seem to be true in TEF. The occurrence of other anomalies (particularly the Vater association[3]) with TEF suggests a teratogen or genetic makeup that may influence several systems; the cardiovascular[4] and gastrointestinal systems[5] are most often involved.

We are aware of two reports of tracheoesophageal fistula in mother and child.[6,7] The malformation has occurred in identical twins,[8,9] but many identical twins have been born with only one of the twins having the anomaly.[10] Brothers, sisters, cousins, and brother-sister combinations with TEF have been described.[11] Further study of children born to parents who had TEF may give additional insight into the influence of heredity as an etiologic factor.[12]

We conducted an informal mail survey of the chiefs of service of 14 major pediatric surgical centers in North America that treat a total of 125 to 150 patients with TEF per year. No cases of TEF in parent and child could be remembered as having occurred in these institutions over a ten- to 25-year period, although no formal review of clinical records was carried out.

When a family history of TEF exists, the pediatrician should be quick to rule out an esophageal atresia by the passage of a nasogastric tube under fluoroscopic control; this is almost always diagnostic by showing it curling in the blind pouch. A barium swallow and/or endoscopy is needed for the diagnosis of an H-type fistula.

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1. Haller JA: Tracheoesophageal fistula and esophageal atresia, in Schwartz SI, Lillehei RC, Shires GT, et al (eds): *Principles of Surgery.* McGraw-Hill, New York, McGraw Hill Book Co, 1974, pp 1516-1521.

2. Gray WW, Skandalakis JE: *Embryology for Surgeons.* Philadelphia, WB Saunders Co, 1972, pp 66-79.

3. Barry JD, Auldist AW: The Vater association. *Am J Dis Child* 128:769-771, 1974.

4. Greenwood RJ, Rosenthal A: Cardiovascular malformations associated with tracheoesophageal fistula and esophageal atresia. *Pediatrics* 57:87-92, 1976.

5. Andrassy RJ, Mahour H: Gastrointestinal anomalies associated with esophageal atresia or tracheoesophageal fistula. *Arch Surg* 114:1125-1128, 1979.

6. Dennis NR, Nicholas JL, Kovar I: Oesophageal atresia (three cases in two generations). *Arch Dis Child* 48:980-982, 1973.

7. Engel MA, Vos LJ, DeVries JA, et al: Esophageal atresia with tracheoesophageal fistula in mother and child. *J Pediatr Surg* 5:564-565, 1970.

8. Blank RH, Prillaman PE, Minor GR: Congenital esophageal atresia with tracheoesophageal fistula occurring in identical twins. *J Thorac Cardiovasc Surg* 53:192-196, 1967.

9. King SL, Ladda RL, Shocat SJ: Monozygotic twins concordant for tracheo-esophageal fistula and discordant for the Vater association. *Acta Paediatr Scand* 66:783-785, 1977.

10. Haight C: Some observations on esophageal atresia and tracheoesophageal fistulas of congenital origin. *J Cardiovasc Thorac Surg* 34:141-172, 1957.

11. Kalicinski Z: Symposium on esophageal atresia. *Z Kinderchirurgie* 17:42-46, 1975.

12. Schimke RN, Leape L, Holder TM: Familial occurrence of esophageal atresia: A preliminary report. *Birth Defects* 8:22-23, 1972.

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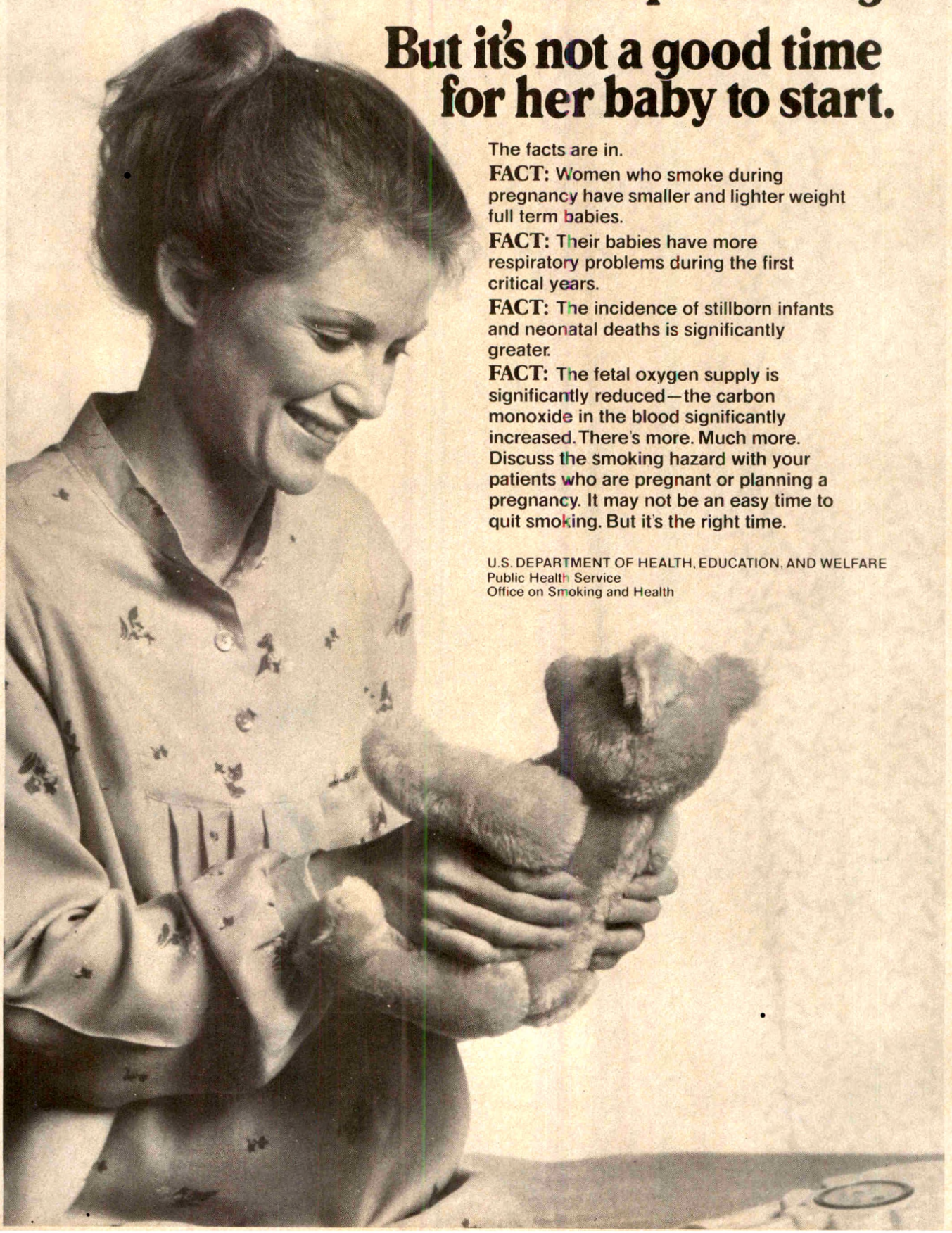
But it's not a good time for her baby to start.



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FACT: The incidence of stillborn infants and neonatal deaths is significantly greater.

FACT: The fetal oxygen supply is significantly reduced—the carbon monoxide in the blood significantly increased. There's more. Much more. Discuss the smoking hazard with your patients who are pregnant or planning a pregnancy. It may not be an easy time to quit smoking. But it's the right time.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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NOW PETER

Attention Deficit Disorders* under control...
His natural abilities are coming through

Now Peter's enjoying more things at play as well as in school. He works better with his teacher and classmates... likes doing things with his dad... gets more natural pleasure out of family and friends.

Now that his concentration is improved, his natural abilities are coming through. He's functioning better. Under a well-integrated program of treatment for Attention Deficit Disorders (ADD), hyperactivity and impulsiveness are markedly reduced.

Ritalin (methylphenidate) can be a vital part of his regimen. With adjunctive use of Ritalin, many ADD children are better able to control hyperkinetic behavior —act in a more natural and appropriate manner.

A 20-year record of proven efficacy

Over the years, Ritalin has become an established choice for pharmacotherapy of ADD. In a report by the

BEHAVES MORE NATURALLY.

National Council on Child Health,[1] Ritalin was described as among the most effective and best-documented agents for stimulant therapy in hyperkinetic children.

Reduces hyperactivity, impulsive behavior

Ritalin has a well-documented record of success in relieving the dominant symptoms of ADD. As it reduces distractibility, disorganized behavior and hyperactivity, improved school performance usually results,[2,3] as well as better peer interaction.[2]

Generally well tolerated

Although side effects may occur with Ritalin, they are generally not serious. During prolonged therapy, anorexia, weight loss, and insomnia are among the most frequently encountered adverse reactions. (See Adverse Reactions section of the prescribing information.) Even though most children require long-term treatment, there is little evidence of habituation.[1]

Therapy with Ritalin should be considered only after a medical diagnosis of ADD has been confirmed. Dosage can usually be interrupted during weekends and vacations. In some cases, these drug holidays reveal "stabilization" in the child's behavior without medication. They may permit a reduction in dosage and eventual discontinuation of drug therapy if warranted.

*Attention Deficit Disorders: new designation by the American Psychiatric Association; formerly called Minimal Brain Dysfunction (MBD) or Hyperkinetic Syndrome.

Ritalin . . . only when medication is indicated for Attention Deficit Disorders

Ritalin® C II
(methylphenidate)
as adjunctive therapy for ADD

Ritalin® C II
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Only when medication is indicated

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TABLETS

INDICATIONS

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span; distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug and in patients with glaucoma.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

The Ritalin tablets (5 and 20 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Children (6 years and over)

Start with small doses (*eg*, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Tablets, 20 mg (peach, scored); bottles of 100 and 1000.

Tablets, 10 mg (pale green, scored); bottles of 100, 500, 1000 and Accu-Pak® blister units of 100.

Tablets, 5 mg (pale yellow); bottles of 100, 500 and 1000.

Dispense in tight, light-resistant container (USP).

665382 C80-14 (1/80)

Consult complete product literature before prescribing.

References

1. Kugel RB, Scherz RG, Seidel HM, et al. Council on Child Health. Medication for hyperkinetic children. *Pediatrics* 1975 (Apr.); **55**(4) 560-562.
2. Hoffman SP, Engelhardt DM, Margolis RA, et al. Response to methylphenidate in low socioeconomic hyperactive children. *Arch Gen Psychiatry* 1974 (Mar.); **30** 354-359.
3. MacKay MC, Beck L, Taylor R. Methylphenidate for adolescents with minimal brain dysfunction. *NY State J Med* 1973 (Feb.); **73** 550-554.

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Letter From Abroad

Great Expectations

London.—An obstetrician I have the good fortune to work with from time to time telephoned me with a curious and novel problem. A foreign lady, aged 31 years and expecting her first baby in about four weeks, had consulted him about her forthcoming confinement. Not having seen her previously, he quite properly arranged for her to have an ultrasound scan. Clinically, her condition was unremarkable, but the scan showed a large swelling on the anterior abdominal wall of the fetus, correctly interpreted as highly suggestive of an exomphalos, omphalocoele, or gastroschisis. The scan had been performed in a highly respected department by experts using the latest equipment. The question now was—or rather, the questions now were—what further investigations should be made, should she be delivered after an induction or by an elective section two or three weeks before term, and how much should he tell the parents?

Prenatal detection of fetal abnormality is a mixed blessing, and the problems raised by such unexpected findings late in an otherwise normal pregnancy are likely to be encountered more often with the development of high-resolution ultrasound imaging. Its usefulness in detecting neural defects, hydrocephaly, and microcephaly is already well established. Less clear is what to do about cystic kidneys or an enlarged liver. The discovery of an exomphalos was new to both of us.

The question of further tests was relatively easy to resolve. Both serum and amniotic fluid α-fetoprotein levels would probably be elevated, but even if the tests discriminated reliably between normal and abnormal babies at 36 weeks' gestation, knowing the levels did not seem to offer any immediate practical application. In days happily gone by, we used to show the fetal intestine by putting a contrast medium into the amniotic sac before doing an intrauterine transfusion for severe Rhesus haemolytic disease. The same technique would presumably demonstrate loops of bowel that have spilled out of a defect in the abdominal wall provided they are not obstructed and viable, but roentgenograms during pregnancy are not respectable any more and paediatric surgeons often overreact to the presence of contrast material in the bits they operate on, as do anaesthetists.

The discussion about the mode of delivery was prompted by the obstetrician's fear that he might rupture the sac—or rather, that the sac might rupture spontaneously during the birth. The risk would presumably be less with a smaller baby, and less still if the delivery were by an elective cesarean section one or two weeks before term, or earlier if she went into spontaneous premature labour. The question hinged on whether such sacs ruptured during labour and, like most paediatricians, my total experience of some half-a-dozen cases was not enough to go by. In the course of more than 20 years' practice, I have often been astounded by the immense swellings that have run the gauntlet of the human female birth canal and remained intact—myelocoeles, encephalocoeles, omphalocoeles, and even conjoint twins. I have also seen severe gastroschisis with herniated liver and spleen and masses of unhealthy purple intestine, but in which any sac had disappeared long before the delivery. I promised to put the question to our paediatric surgeon, but before I had the chance to do so the patient was admitted in early labour.

The good Boy Scouts' motto is to "Be Prepared." Caught distinctly unprepared by the unexpected onset of a few contractions, the wisest plan seemed to be to postpone labour while the hitherto leisurely process of decision making proceeded at a more pressing pace. The question of what to say to the parents depended on whether any intervention was planned. It was agreed that honesty was the best policy and that patients are entitled to be adequately informed about their state of health. On the other hand, ignorance can be bliss and silence golden. The lady was not English, and a condition such as a gastroschisis could take a lot of explaining. It was clearly unthinkable to subject her to a cesarean section without telling her why, but there was much to be said for keeping quiet about the results of the ultrasound scan if she was to go through a normal labour.

Her contractions ceased and she fortunately went out of labour as our paediatric surgeon confirmed that omphalocoeles rarely rupture during delivery and that those which had ruptured probably did so long before labour. Based on an analysis of his last 70 cases, his experience was reassuring. The discussion had the added benefit of forewarning him of a possible emergency repair now seemingly done with sterile dura specially imported from German crania and he hastened to the operating room to make sure he had an adequate supply in stock.

The following week, the membranes ruptured and she went into labour. As happens in all good fiction on these occasions, an obstetrician, an anaesthetist, and a paediatrician converged on the labour ward at 2 AM. The choice of physician over surgeon at the delivery had been dictated by several elementary considerations. It is not difficult to wrap up a bit of omentum on a temporary basis, but skillful resuscitation is not everybody's forte, and who but a physician would recognise whether the baby had a chromosomal disorder or other congenital abnormalities? A selection of clear, plastic, nonadherent sterile dressings had already been purloined from the operating room, there was a "silver swaddler" on the resuscitation trolley, and I had a roll of unsterile but microbially irreproachable "cling-film" sandwich-wrap in my car.

One of the pleasures of having to

attend a delivery at 2 AM in recent years is the tranquil atmosphere promoted by a good obstetrician and a good anaesthetist. Gone are the days of maternal distress, cries of anguish, and the shouting of people exhorting some poor woman to push or not push as the case may be. Epidural analgesia must surely be one of the greatest blessings bestowed on women of childbearing age by modern medicine and the curious fanaticism for "natural childbirth" by some is quite incomprehensible to me. Its one occasional drawback as far as I am concerned is that it has encouraged the presence of fathers at deliveries. A few agonising screams would soon drive them to the most distant part of the building, but now that mothers are wreathed in smiles under the blissful relief of an effective epidural, they jollificate in their sport coats, cameras in one hand and often a drink in the other, as if it were some kind of birthday party, which of course it is. I admit I am prejudiced, but the trouble with being a paediatrician is that we see the abnormalities—the sudden catastrophes for which most fathers seem to be totally unprepared.

This particular father was exceptional in that he looked anxious, apprehensive, subdued, and thoroughly ill at ease. If anything, he looked even more so when he realised that a paediatrician had been called in. He went and sat miserably by himself in a corner, but cheered up a little when I told him that I was merely there to make sure I should have no work to do. Normal babies cannot be had to order and abnormalities sometimes happen, but I said that it was an inexplicable fact that my services were usually superfluous when I was present and urgently needed when I was not. He seemed reassured by this unscientific explanation and said nothing more until it was all over, when he shook my hands effusively and could not thank me enough, as if it had all been my doing.

The baby, incidentally, a 2,912-g (6½-lb) girl, was perfectly normal—an eventuality that we had not considered. If there is a moral, and I am not saying there is, it is surely:

It is better to do nothing than to do something when nothing should be done.

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Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

Drug Advertising

Sir.—I am concerned that two drugs that have been judged to lack effectiveness are being advertised in the JOURNAL. Actifed-C and Tuss-Ornade had been evaluated by proper committees of the National Academy of Sciences more than a decade ago and found ineffective for any indication. Yet they have been advertised in the JOURNAL month after month, influencing pediatricians and residents. The advertising copy of all carry the legend that "there is a lack of substantial evidence that this . . . drug has the effect purported."

What this means is that the AMA's official journal carries advertisements for drugs that are ineffective. Both drugs were also branded "irrational mixtures" by the AMA itself in 1971.

Whereas the drugs do not have efficacy, their side effects are real and can be serious. The risk-to-benefit ratio is unacceptably high—in brief, the drugs do no good, but may cause a lot of harm. Should the official journal of the AMA continue advertising these drugs? I think not.

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In Reply.—Mr Barna is not correct in stating that Actifed-C and Tuss-Ornade were found by committees of the National Academy of Sciences to be ineffective for any indication. If this had been so, then these drugs would have been withdrawn from the market by the Food and Drug Administration (FDA). The judgment made was that the effectiveness of these drugs was not proved by clinical trials conducted by experts. The companies that market these drugs have been permitted by the FDA to continue to market them for a limited period of time or until their effectiveness has been proved by controlled clinical trials. The advertisements for these drugs carries the notice that there is lack of substantial evidence for the effect purported, but this does not prove that they are ineffective. The AMA Council on Drugs adopted a position in the early 1970s that "drug combinations are irrational." Such a sweeping condemnation appears to many physicians to be itself irrational.

Mr Barna states that the risk-to-benefit ratio for these drugs is unacceptably high, but offers no supporting data for such a judgment. Obviously, more experienced evaluators of drugs convened by the National Academy of Sciences and also those employed by the FDA disagree with Mr Barna, for these drugs were not removed from the market.

When all the evidence is in and the final judgment arrived at, the AMA will respect that judgment in acceptance of advertising.

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Hyperuricemia in Cyanotic Congenital Heart Disease

Sir.—The report by Dearth et al (JOURNAL 132:900-902, 1978) called attention to the hyperuricemia that occurs with secondary polycythemia in patients with congenital cyanotic heart disease. Although the pathogenesis of the arthritis, nephropathy, and urolithiasis in primary gout appear to be related to the duration of exposure to hyperuricemia and degeee of elevation of serum urate concentration,[1] the same conclusion cannot necessarily be reached in those patients with hyperuricemia that results from polycythemia secondary to cyanotic heart disease.

In an earlier publication on the natural history of 57 patients with the

Eisenmenger syndrome,[2] hyperuricemia (7 mg/dL to 12 mg/dL; mean, 10.5 mg/dL) was present in all of those in whom serum uric acid determinations were made, namely seven patients in the original communication and 19 obtained subsequent to publication. Despite comparably high hematocrit and serum uric acid levels, of 41 patients either first seen as adults or followed from childhood into adult life (up to 18 years of age; average, 5 years), in only two men, aged 25 and 32 years, did acute gouty arthritis develop. Although this 5% incidence in a small sample is higher than that in the Framingham study,[1] in which the incidence was 0.2% at a mean age of 44 years and 1.5% at a mean age of 58 years, it still suggested to us that an heritable predisposition (polygenic?) to gout,[3] in addition to the polycythemia and resultant hyperuricemia, is required.

The overall incidence of urolithiasis in primary gout has been reported as 22% by Yü and Gutman[4] and as high as 40% in men at serum uric acid levels of 9 mg/dL or greater.[1] In secondary gout, the reported incidence is 42%.[4] None of our 57 patients, however, showed evidence of calculi over the period of observation.

Fifteen subjects were examined postmortem. Four were children between the ages of 9 and 14 years, five young adults aged 17 to 23 years, and six older adults ranging from 34 to 58 years. Similar to the report of Somerville,[5] none showed nephropathic change attributable to the hyperuricemia.

While admittedly the Mayo Clinic study was retrospective and offered no follow-up as to the eventual development of gouty arthritis, urolithiasis, or nephropathy in their patients, our data suggest that these manifestations are relatively uncommon sequelae. I question, therefore, the recommendation of a therapeutic trial of allopurinol to lower the serum uric acid level, inasmuch as the risk of these complications of hyperuricemia does not seem to be so "real," nor is the use of allopurinol in hyperuricemic states so "safe" as they postulate.

Side effects from the use of allopurinol may occur in about 20% of all patients.[6] Some may be extremely serious and occasionally fatal. Toxic manifestations reported have included gastrointestinal intolerance, alopecia, bone marrow suppression, hepatitis, vasculitis, and drug rashes. The latter are apparently more frequent and serious in patients receiving both allopurinol and ampicillin, an antibiotic commonly used in pediatric practice.

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1. Hall AP, Barry PE, Dawber TE, et al: Epidemiology of gout and hyperuricemia: A long-term population study. *Am J Med* 42:27-37, 1967.
2. Young D, Mark H: Fate of the patient with the Eisenmenger syndrome. *Am J Cardiol* 28:658-669, 1971.
3. Wyngaarden JB, Kelly WN: Gout, in Stanbury JB, Wyngaarden JB, Frederickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 4. New York, McGraw-Hill Book Co Inc, 1978, pp 974-976.
4. Yü TA-F, Gutman AB: Uric acid nephrolithiasis in gout: Predisposing factors. *Ann Intern Med* 67:1133-1148, 1967.
5. Somerville J: Gout in cyanotic congenital heart disease. *Br Heart J* 23:31-34, 1961.
6. Wyngaarden JB, Kelly WN: Gout, in Stanbury JB, Wyngaarden JB, Frederickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 4. New York, McGraw-Hill Book Co Inc, 1978, pp 990-991.

Childhood Brachial Plexus Neuropathy

Sir.—We enjoyed reading the recent paper by Charles and Jayam-Trouth regarding brachial plexus neuropathy (BPN) in childhood (JOURNAL 134:299-300, 1980). We also have had experience with this disorder and agree that an infectious cause seems likely, particularly in patients with CSF pleocytosis.

However, we disagree with the authors' conclusions that childhood BPN has a uniformly excellent prognosis. We recently reported on two children with BPN and one of them, a girl with onset at age 1 year, has had no functional improvement over a two-year follow-up period.[1] The child's left arm remains completely useless and extensive atrophy has occurred. We are also concerned about the authors' case 3, who has shown little improvement of limb weakness in the interim between the six-month and one-year examinations.

Childhood BPN seems to be an uncommon disorder, and despite occasional case reports in the literature the extent of our knowledge remains limited. Although the prognosis of adult BPN has been established with some certainty,[2] we must use caution in extrapolating these results to children. Until a study comparable to that published by Tsairis and co-workers[2] critically examines this entity in childhood, we should not consider the prognosis of childhood BPN to be excellent in all cases.

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1. Bale JF Jr, Thompson JA, Petajan JH, et al: Childhood brachial plexus neuropathy. *J Pediatr* 95:741-742, 1979.
2. Tsairis P, Dyck PJ, Mulder DW: Natural history of brachial plexus neuorpathy. *Arch Neurol* 27:109-117, 1972.

Reye's Syndrome and Pancreatitis

Sir.—The report by Ellis et al in the JOURNAL (133:1014-1016, 1979) describing the postmortem finding of acute pancreatitis in four of 18 children with Reye's syndrome led us to determine the frequency of acute pancreatitis in our patients with this syndrome. The records of 27 such patients hospitalized in Albany Medical Center Hospital, Albany, NY, during 1971 through 1979 were reviewed. Postmortem examination was performed in six of the 11 subjects. Acute diffuse interstitial pancreatitis was found in one subject, a boy. Serum amylase level determined during the acute illness in three patients who survived was within the normal range.

Although an association between Reye's syndrome and acute pancreatitis no doubt exists,[1,2] the reason for this association remains unclear. It is possible that in Reye's syndrome, as well as in other diseases with hepatic dysfunction, the acute liver failure is the cause for the pancreatitis.[3,4]

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1. Chaves-Carballo E, Menezes AH, Bell WE, et al: Acute pancreatitis as a fatal complication in Reyes syndrome. *Pediatr Res* 13:523, 1979.
2. Gilboa N: Idiopathic acute pancreatitis in children. *Am J Dis Child* 129:984, 1975.
3. Geokas MC, Olsen H, Swanson V, et al: The association of viral hepatitis and acute pancreatitis. *Calif Med* 117:1-7, 1972.
4. Parbhoo SP, Welch H, Sherlock S: Acute pancreatitis in patients with fulminant hepatic failure. *Gut* 14:428, 1973.

Books

Pregnancy Metabolism, Diabetes and the Fetus: Ciba Foundation Symposium No. 63 (New Series), 326 pp, $39.50, Amsterdam, Excerpta Medica, 1979.

This book is an excellent compendium on maternal and fetal metabolism, their interrelationships, and the resultant perturbations on this unit caused by diabetes. There are 13 chapters, all of which are followed by a discussion, written by 26 well-recognized authorities in this field. Initial sections focus on normal maternal metabolism, transplacental substrate fluxes, and normal fetal nutrition. These chapters provide a smooth transition to two highly culled topics among many possibilities, namely, the hormonal regulation and induction of hepatic and placental enzymes. Remaining sections cover altered fetal metabolism secondary to maternal diabetes and its eventuality, in particular, in perinatal morbidity and congenital malformations. Each chapter and its discussion are replete with information, and all are well referenced and well written—despite the confusing use of pregnancy as an adjective in the book's title. The ensuing interchange of ideas by the collaborators is delightful, provocative, seemingly unedited, and occasionally vitriolic. I enjoyed listening in on such a brisk flow of data and concepts as the authors explicated or debated an issue.

This symposium on maternal diabetes is not for the general clinician who is seeking a differential diagnosis, workup, information on the controversies surrounding different therapeutic interventions, or long-term prognosis. This is by no means a comprehensive text for the management of diabetic pregnancy but rather a reservoir of information, providing a conceptual framework with which to approach this abnormal metabolic state. Unfortunately, the index is incomplete and often inconsistent. For example, several enzymes discussed in the text are readily found in the index but, for no apparent reason, many are not (glucose-6-phosphate dehydrogenase, acetyl CoA carboxylase, etc). Other neonatal complications of maternal diabetes of interest to the pediatrician, and quite controversial in etiology, include polycythemia, hypocalcemia, and renal vein thrombosis, all of which are overlooked in this book. Moreover, a couple of chapters consist entirely of the author's research, presented as a journal article.

The above-mentioned concerns are far outweighed by the scientific scholarship and expertise of the contributors, making this book a necessity for those interested in normal maternal metabolism and the chronic somatic and biochemical adaptations by the fetus to maternal diabetes.

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Outlines of Muscular Dystrophy, by Yves M. Rideau, 160 pp, $17, Poitiers, France, Faculte De Medecine, 1978.

This monograph was written with the express purpose of disseminating simple, practical knowledge about muscular dystrophy. It was originally published in French and is distributed by the French Muscular Dystrophy Association.

The discussion is limited to three major genetic groups of muscular dystrophies: the sex-linked form represented by the severe Duchenne's and benign Becker's types, the autosomal recessive form represented by the limb-girdle type, and the autosomal-dominant form represented by the facioscapulohumeral type.

Well-presented illustrations and statistics cover most aspects of these forms of muscular dystrophy. They may be useful as background material in discussion with patients.

Unfortunately, the text is frequently redundant, poorly edited, and contains many typographical errors. The translation often contains gallicisms that make the book difficult to read at times.

The discussion of the literature lacks depth. This reduces the book's usefulness for more advanced professionals in the field of myopathies. A further limitation is the description of orthopaedic appliances that differ from those used in the United States.

The book may be a good primer for beginning medical students and health professionals, but has no direct value for experienced neurologists except for its excellent illustrations and useful statistics.

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Care of the High Risk Neonate, ed 2, by Marshall H. Klaus and Avroy A. Fanaroff, 437 pp, $19.50, Philadelphia, WB Saunders Co, 1979.

A former Chief Editor observed in this JOURNAL that "when, from time to time, a comprehensive treatise is written covering a field where such a treatise was needed, a welcome note is always sounded when a second or subsequent edition erupts." It seems only a few years ago that there existed no more than a few books relating to the management of newborn infants. Within the past decade, numerous treatises have been developed to meet this need, some with greater success than others. Among the most successful and the most widely used has been the first edition of the present book, and, not surprisingly, the second edition is bigger and better than the first. This edition has 20% more pages; extensive revisions have been included; a new chapter on antenatal and intrapartum care has been added; and the number of contributors, editors, and commentators has been doubled.

It is customary in describing multiauthored textbooks to comment on the uneven quality of the chapters written by different authors. The consistency in content and format from chapter to chapter throughout this book could only be the result of strong guidance and supervision by the editors. The editors had a clearly defined purpose in preparing a book that provided "a sound physiologic basis for current

perinatal practice," and they have succeeded in achieving this goal. An approach to the care of high-risk neonates and their families is presented, not in cookbook fashion, but by presenting and building on existing biochemical, physiologic, and behavioral information.

A critical synthesis of science and practical wisdom is presented, including such examples as, "the temperature of the delivery room is frequently set for the comfort of the medical staff rather than that of the newborn;" regarding infant feeding, "beware of any new preparation;" and when talking to the father of a recently transferred infant, "a cup of coffee and a quiet chat are most useful." Though the emphasis is on the high-risk infant, the needs of the normal newborn infant are not ignored. The appropriate use of charts, tables, illustrations, and pertinent references makes this a useful handbook for anyone involved in the care of newborn infants. Numerous procedures, including such practical concerns as the securing of orotracheal tubes, the insertion of umbilical-vessel catheters, and the progression of feedings in very low-birth-weight infants (< 1,250 g) are presented in detail.

A textbook by its very nature requires that existing information be presented from a specific and, oftentimes, dogmatic point of view. As a method of presenting conclusive points of view and at the same time indicating the uncertainties of these positions, the editors have invited outside experts in pediatrics and obstetrics to comment on the text and to present their opinions, which sometimes agree but often conflict with those of the authors. It is in part because of this public debate in conversational style that this book is frequently referred to as being "fun", a term that can be applied to few medical textbooks.

As can be expected with any summary of clinical management, this book includes approaches to some problems that will not satisfy every reader. But the differences of opinion are less important than the overall perspective of newborn care provided in this manual. This book describes in a lucid manner the care of high-risk newborn infants, based on the information available at this time. It is an informative and useful manual for medical students, pediatric residents, nurses, and pediatricians, including neonatologists. It is deserving of a position on the list of pediatric best sellers.

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History of American Pediatrics, by Thomas E. Cone, Jr, 278 pp, 68 illus, $18.95, Boston, Little Brown & Co, 1979.

This volume represents a milestone in the study of child health and welfare in the United States. Its appearance is appropriate, as Samuel Radbill notes in the foreword, at the end of the International Year of the Child and in time for the golden anniversary of the American Academy of Pediatrics. The book does not fail this auspicious setting: it is attractive, well researched, lucidly written, and adequately illustrated. The publisher has added an attractive format, beautiful and easily read type, and faithful reproduction of photographs, which should please a wide audience.

The study is divided into three periods: colonial, with chapters on pastor- and governor-physicians, children discovered, and feeding colonial infants; the 19th century, with chapters entitled "Perplexing Obscurity and Embarrassing Uncertainty," "Explorers in an Almost Unknown Country," and "Infant Feeding of Paramount Concern"; and the 20th century, with chapters "Pediatrics Comes of Age," "Antibiotics and Electrolytes," "The Changing Face of Pediatrics," and "From Complexity to Simplicity." Each chapter concludes with representative but not exhaustive references, and the entire volume is indexed by name and subject. Lists of pediatric textbooks or other new publications are included; in the first two sections the historian speaks through the current observers by skillfully weaving their writings into the text.

Years ago, I had a long, continued debate with James A. Ford, then anthropologist at the American Museum of Natural History, New York. The subject was whether human culture swept along on its own initiative, producing leaders by inherent momentum, or whether leaders in thought and action altered culture and produced history. Cone follows the humanistic viewpoint and offers his present history largely through its leaders, not through the story of movements and organizations. The majority of the illustrations are photographs of leading men (plus two women, Josephine Baker and Virginia Apgar, which seems to slight women like Grace Abbott, Julia Lathrop, Katherine Bain, Edith Lincoln, Helen Taussig, and Mary Ellen Avery).

The story of colonial pediatrics is a litany of childhood illness and death, monotonous for three centuries because of medical ignorance and social neglect. The chief breaks in the litany are the interesting accounts of the pastor-physicians and governor-physicians, the progressive delineation of infectious diseases, and the significant story of smallpox inoculation by Boylston at the instigation of Cotton Mather. Some apology is due to our neighbors: the book's title preempts "American pediatrics" for the United States, to the exclusion of Canada and the Latin American countries, many of which had cities, universities, hospitals, and medical schools long before this country did. Moreover, Cone looks at colonial United States through English eyes and from the Atlantic Coast, forgetting the French settling of the St Lawrence, the Great Lakes area, and the Mississippi valley to Louisiana and Mobile, and the Spanish colonial empire in Florida, Texas, and the Southwest, with settlements like St Augustine and Santa Fe that antedated the English period.

Reflecting the bias of the earlier historians toward other races, little is said about the devastating effect of slavery on the health and welfare of black children, or the crushingly horrible result of European diseases on the totally susceptible American Indian. The latter can be inferred from notations in historical accounts, from the archaeological record of the past 50 years, from recent accounts of Carlton Gajdusek (who described the ravages of chickenpox among the Indians coming out of Paraguay's Gran Chaco), and the recent decimation of the Yanomamo by measles. Almost total obliteration of peoples and cultures may have occurred. Elvas, a chronicler of the DeSoto expedition, records that in 1540, on arrival of the army at Cofitachequi on the Savannah River, "Within a league and half about this towne, were great towns dispeopled and overgrown with grasse....The Indians said that two years ago there was a plague in that countrie...." Westward, DeSoto encountered many populous towns, but when the French

reached the lower Mississippi valley during the next century, scant traces of these populations remained, a finding confirmed by archaeologists. John Smith stated, "God had laid this Country open for us, and slain the most part of the inhabitants by civill warres and a mortal disease, for where I had seene one hundred or two hundred Salvages, there is scant ten to be found...." Du Pratz noted that the nations of Louisiana were once both numerous and populous, but were then "thinned and diminished" by distempers that included smallpox and a cold (influenza?).

The 19th century is marked during its early part by continued ignorance and high mortality (including terrible diarrheas) as the cities grew larger and less sanitary, by new epidemics (yellow and typhoid fevers, cholera, and malaria), but also by the advent of a few physicians interested in children. There were DeWees (still famous in the early years of my practice for DeWees carminative), the Meigs, and Benjamin Waterhouse, who introduced Jenner's cowpox vaccine to the United States. The latter half of the century saw pediatrics emerge as a specialty, beginning with Abraham Jacobi and Job Smith; Rotch and Emmett Holt followed. Holt's classic *The Care and Feeding of Children* and his textbook were standard during my medical school years at Tulane and in my early practice.

The 20th century opened with biochemistry. The eccentricities of percentage formulas were pediatric foibles by the time of my residency in 1930, replaced by the pragmatism of Marriott and Brennemann, and made redundant by the miracles of sanitation, refrigeration, and the expertise of dairymen and milk processors—too often unsung. Dr Cone might have shifted some of the emphasis from formulas to nutritionists, with the discovery and synthesis of vitamins (one of his rare errors is the statement that, in 1926, Goldberger and colleagues reported the discovery of riboflavin and identified it as the antipellagra factor).

I saw pellagra, rickets, beriberi, scurvy, hypoproteinemia, and hypoprothrombinemia in Louisiana during the 1920s and 1930s, among low-income families on restricted diets of canned foods and refined cereals. They had departed from the rich and varied supplements of native foods—fruits, berries, greens, nuts, wild game, and fish—of the forests, lakes, and fertile valleys of the Gulf coastal plain and the great rivers, which had abundantly sustained Indians, then whites and blacks, for untold centuries.

The other pediatric marvels are all in this volume: antitoxins, vaccines, and antibiotics; steroids and antimetabolites, endocrinology and hematology, transfusions and infusions, rehydration, and acid-base balance; newborns, prematures, and prenatal diagnosis; surgery and anesthesiology; the conquest of disease after disease; old nightmares and new. The pediatric giants are there to see, and all deserving. One should also view the collection of lesser lights, in offices and clinics, in hospitals, medical schools, and research laboratories, the nurses and technicians, the specialists in other fields, the organizations and foundations, the related industries, the governmental agencies, and the myriads of others who have joined to make the care of its children—not just in the great centers but from coast to coast—one of the crowning joys of our culture.

Cone is correct in saying that a person cannot justly assay pediatric history when he lives in the midst of it, but he can and does glory in it. He joins the other veterans who believe that we have lived through the golden age of pediatrics. He can also join us in apprehension over the new social pathology: family disintegration, child and drug abuse, teenage pregnancy, abortions, and litigation. We can only hope, for the children and those who care for them, that the right answers can be found again.

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The Children of Santa Maria Cauqué: A Prospective Field Study of Health and Growth, by Leonardo J. Mata, 395 pp, $19.95, Cambridge, Mass, MIT Press, 1978.

Students of geographic medicine, nutrition, and human development will find this volume an important addition to their libraries. Dr Mata reports on the extensive and intensive longitudinal study of nutrition and development conducted from 1963 to 1972 in an Indian village in Guatemala. This book details the health of 200 families and especially their developing children over an eight-year period with regard to the microbiologic, nutritional, environmental, and developmental components of general health status. Using multivariate analysis models, the author offers a comprehensive interpretation of the roles of nutrition and infection during pregnancy and early childhood within the natural setting that typifies a majority of the third world.

The health care practices for the newborn and infant provide interesting reading for the perinatologist, and the data provided relating to anthropometry of the newborn, immunoglobulin status, rates of congenital infection, and postnatal growth and health status are exhaustive. Unlike infants in developed countries, third-world infants suffer the combined effects of deficient diets and infection that resulted in a mortality of 576 per 1,000 live births, compared with a mortality of 199 per 1,000 live births in the United States for infants weighing 1,501 to 2,000 g at birth (1972 data); this further strengthens the argument that postneonatal and infant mortalities are strongly related to antenatal influences on fetal growth. Furthermore, the adverse effects of the environment, infection, and undernutrition claim disproportionate tolls, especially in infants of low birth weight.

The biologic and medical data presented in this book are extensive, and the analysis of infant physical growth and maternal and infant nutrition compare favorably with other published studies. The medical anthropologic analysis and public health perspectives offered in the 395 pages would well serve readers whose interests lie in public health, developmental pediatrics, and nutrition.

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Increased Intracranial Pressure in Children, by William E. Bell and William F. McCormick, 485 pp, Philadelphia, WB Saunders Co, 1978.

This monograph is the second edition of a book that was first published in 1972 and is volume 8 in the excellent series, *Major Problems in Clinical Pediatrics*. The major new development of the intervening years was the computerized tomographic (CT) scan; a number of illustrations involving this technique have been added, as

well as a specific section of text. However, the majority of neuroradiologic illustrations continue to be photographs of air studies, which is defensible in that a single picture tells a much better story than a series of blurry CT cuts. I suspect that the third edition will contain CT illustrations of much better resolution, and more of the gross neuropathology will be presented in brain slices that conform to the standard CT image. On the subject of illustrations, it can be said that the monograph is profusely illustrated with excellent quality pictures of patients, pathology, and radiology.

The monograph has been updated and expanded in other areas as well, amounting to a doubling of the pages. For example, whereas Reye's syndrome was handled in one paragraph in the first edition, now it is discussed in more appropriate detail to bring into better perspective what probably amounts to the most common reason for acutely developing brain edema. Reye's syndrome has certainly replaced lead encephalopathy as a prototype cerebral edema problem of childhood. In fact, lead encephalopathy hardly deserves the chapter given to it because of its rarity in current practice. This is an interesting general commentary on medical progress, in this case due to screening programs in many cities for children at risk for lead ingestion. In the same context, if the authors were given an opportunity to reconsider their presentation of herpes simplex encephalitis today, they might give it more than one sentence because of the potential therapeutic effect of vidarabine treatment.

In summary, this is an excellent, well-presented monograph on an important subject and can be recommended as a most useful reference.

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Liver Disorders in Childhood, by Alex F. Mowat, 407 pp, Woburn, Mass, Butterworth Inc, 1979.

This is one of the first texts entirely devoted to pediatric liver disease. Written by Dr Mowat, a pediatrician and pediatric gastroenterologist, it combines a vast clinical experience with a format that is organized to assist the clinician approaching the child who has liver disease. The first few chapters deal exceedingly well with the normal liver of childhood from the standpoints of anatomy, physiology, and assessment of liver size. Though not exhaustive with regard to pathophysiology, the chapters are well referenced and quite up to date. The sections dealing with conjugated hyperbilirubinemia are complete with good tables to assist the physician in differential diagnosis. A discussion of the infectious and metabolic causes of liver disease together with the treatment of cirrhosis and portal hypertension relates to the pediatric experience and, thus, clearly fills a gap in current textbooks devoted to liver disease. The section on diagnostic modalities, particularly the use of newer radio imaging agents and ultrasonography, is short on providing examples and will undoubtedly be expanded in future editions.

In short, this is an excellent, well-written text of general interest to the pediatrician and the gastroenterologist that should serve as a good beginning for students and house staff. The selected current references provide good depth for those interested in further delineation of a particular point. This is an excellent monograph and well worth inclusion in the library.

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60 YEARS AGO IN THE AJDC

Bodily Mechanics: Its Relation to Cyclic Vomiting and Other Obscure Intestinal Conditions

Mobilization of an army to fight as an expeditionary force in Europe had resulted in the examination of 2,570,000 men. Of these, 29.1 per cent. were rejected on physical grounds prior to drafting with one third more rejected after acceptance. The authors contend that much of this lack of fitness would be prevented by greater attention to bodily mechanics in childhood. A study of freshmen entering Harvard University revealed that 80 per cent. of a group of 700 students used their bodies in bad mechanical lines.

Fifteen cases of bad body posture in childhood are reviewed in this study. In each case, physical symptoms attributable to a relaxed posture were improved by exercises, adequate rest, and a body brace. The children ranged in age from 13 months to 10 years and were predominantly males. Symptoms of indigestion, poor appetite, nausea, gassiness, constipation, cyclic vomiting, acidosis, fatigue, and lifelessness were common. In some there was periodic abdominal pain, fever, headache, excessive perspiration, and attacks of diarrhea. Examinations showed poor posture with drooping shoulders, a flared lower rib cage, poor muscle tone, and protuberance of the lower part of the abdomen. Tenderness, suggestive of chronic appendicitis, was sometimes observed and one child was operated upon for acute intestinal obstruction. Roentgen-ray examinations demonstrated gaseous distention of the stomach, dilatation of the small bowel, sagging of the transverse colon, and colonic redundancy.

Treatment in these cases consisted usually of exercises and a routine of rest taken in special positions to correct the faulty mechanics. A body brace with an anteroposterior pad was fitted to the abdomen and back. In several a spring back brace was used. In some, periodic cleansing enemas were administered. Response to the treatment was variable. Some improved quickly, others not for months, or gradually over several years. The authors concluded that this was probably the cause of many if not most cases of recurrent vomiting. They stated that when the faulty mechanics have been corrected, the patients have shown a more speedy recovery than is seen in cases without the correction.—Fritz B. Talbot, Lloyd T. Brown, Boston (20:168-187, September 1920).

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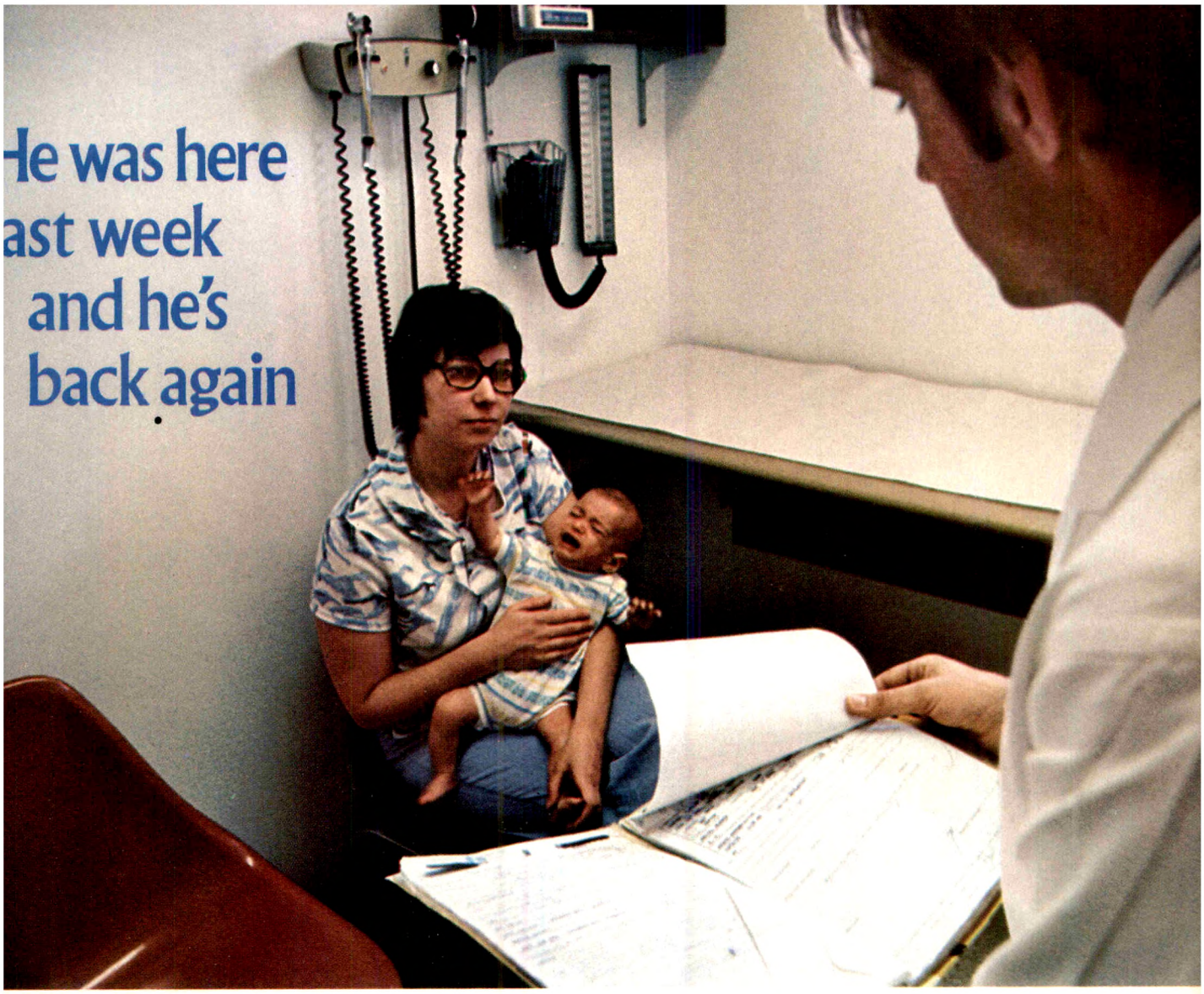

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References: 1. Rapp, D. J.: Milk Allergy — From Birth to Old Age. Consultant 14:120, 1974. 2. Cowan, C.C., Brownlee, R.C., DeLoache, W.R., Jackson, H.P., and Matthews, J.P.: A Soy Protein Isolate Formula in the Management of Allergy in Infants and Children. South. Med. J. 62:389, 1969. 3. Clein, N.W.: Cow's Milk Allergy in Infants and Children. Int. Arch. Allergy, 13:245, 1958. 4. Goldman, A.S., Anderson, D.W., Sellars, W.A., Saperstein, S., Kniker, W.T., Halpern, S.R.: Milk Allergy 1. Oral Challenge with Milk and Isolated Milk Proteins in Allergic Children. Ped. 32:425, 1963. 5. Jung, A.L. and Carr, S.L.: A Soy Protein Formula and a Milk-Based Formula, Clin. Ped. 16:982-985, 1977. 6. Freier, S. and Kletter, B.: Milk Allergy in Infants and Young Children. Clin. Ped. 9:449, 1970.

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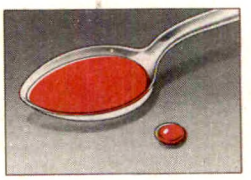

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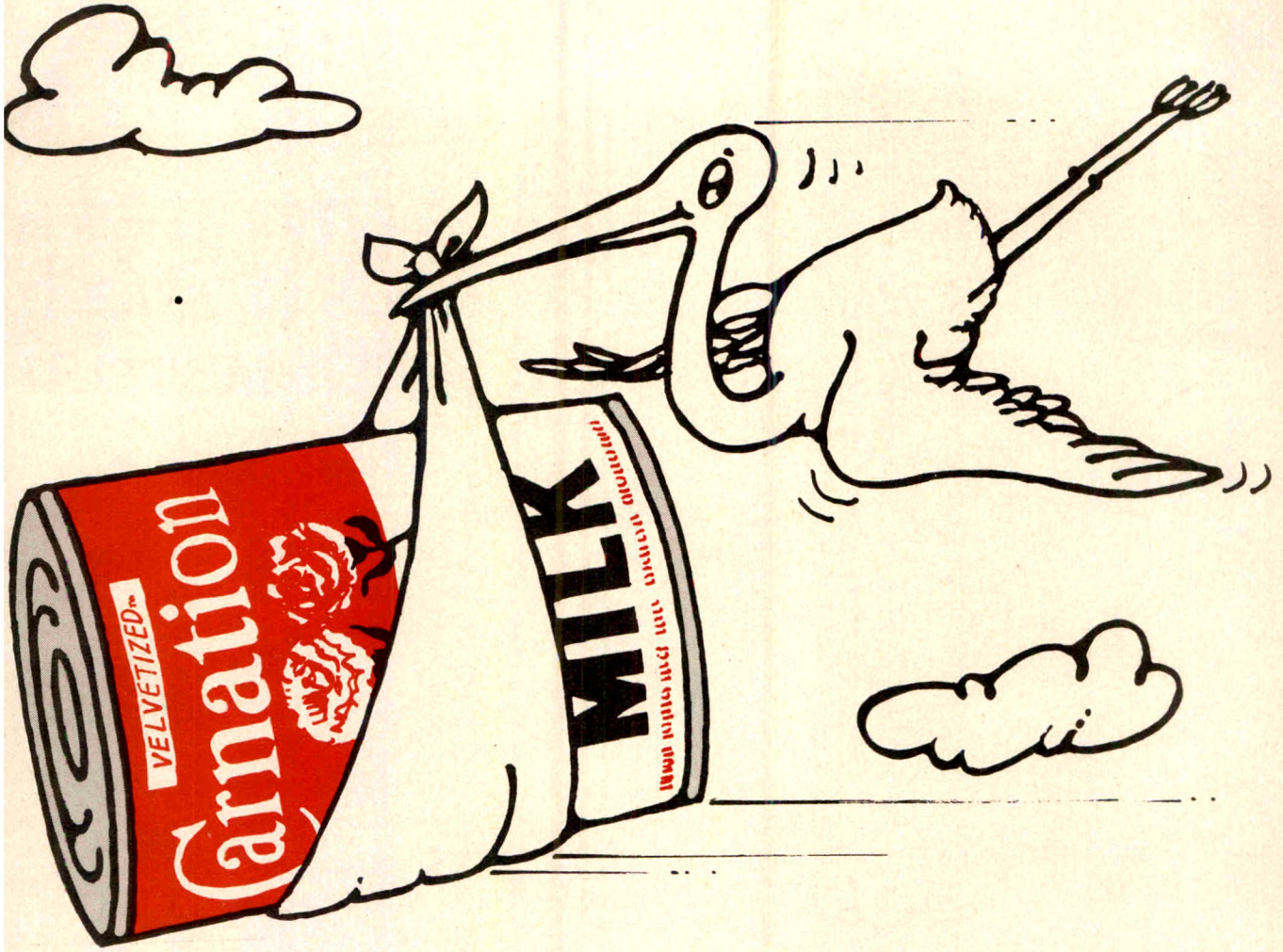

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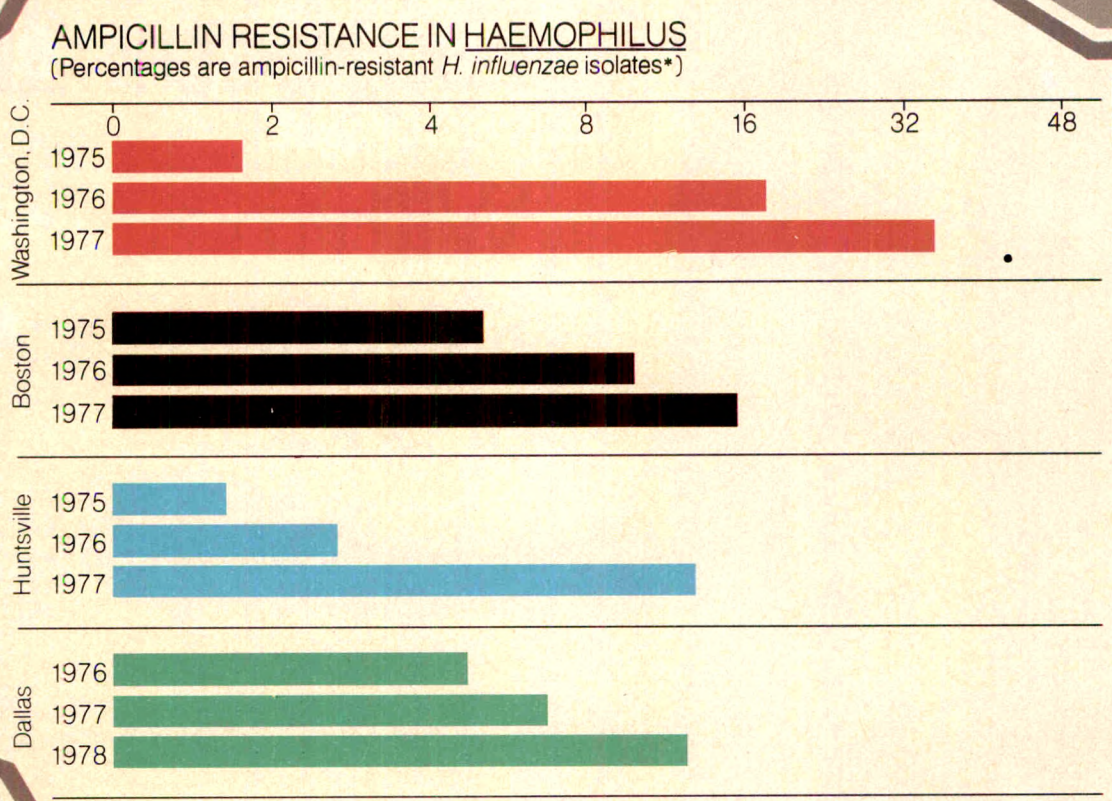

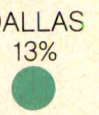

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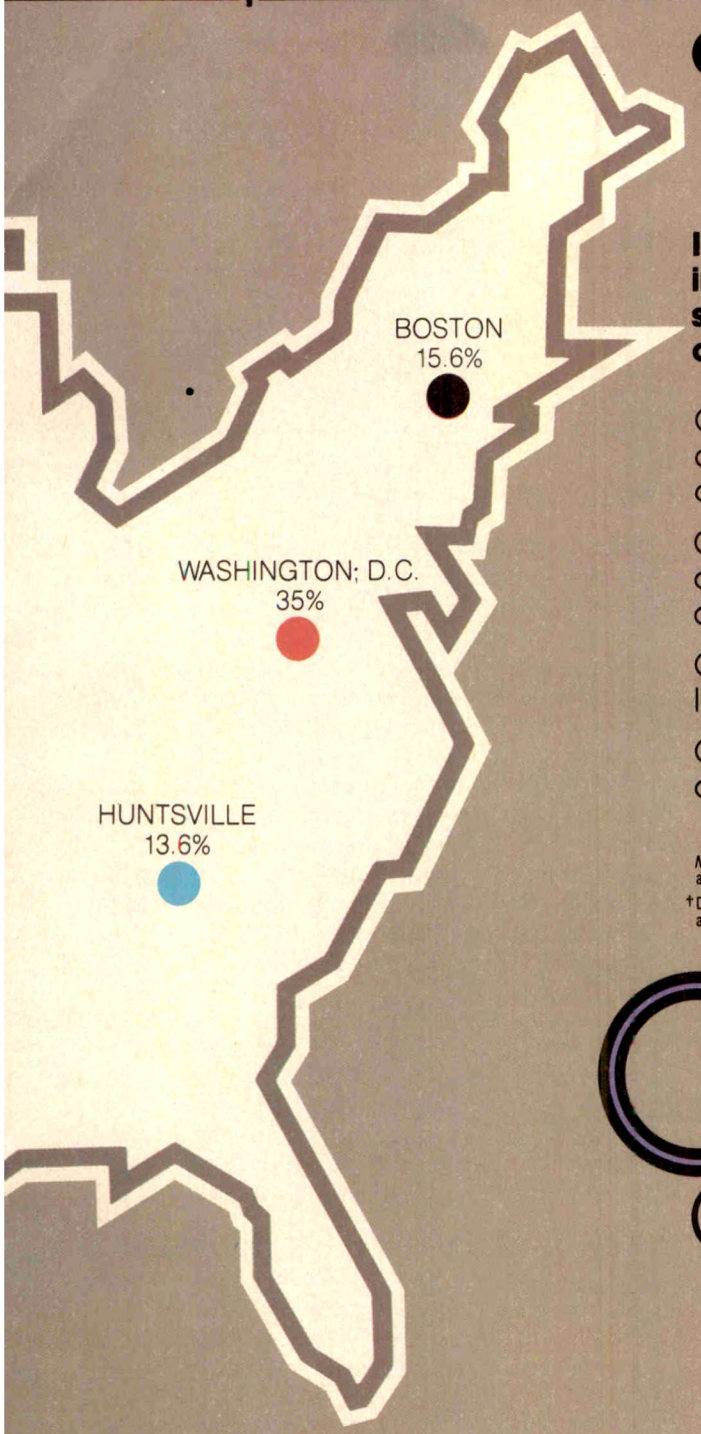

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[0703790]

References

1. J. Pediatr., *92*:889, 1978.
2. J. Pediatr., *94*:983, 1979.
3. J.A.M.A., *239*:320, 1978.
4. Antimicrob. Agents Chemother., *11*:470, 1977.
5. Antimicrob. Agents Chemother., *13*:584, 1978.
6. Antimicrob. Agents Chemother., *12*:490, 1977.
7. Current Chemotherapy, *II*:880, 1978.
8. Antimicrob. Agents Chemother., *8*:91, 1979.
9. Antimicrob. Agents Chemother., *13*:861, 1978.
10. Data on file, Eli Lilly and Company.

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Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 21.6 × 27.9 cm paper. If a table must be continued, use a second sheet and repeat all heads. Each table must have a title.

Uniform Requirements.—Further details on manuscript preparation are given in the document *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* prepared by the International Steering Committee of Medical Editors. Reprints of this document are available by directing requests to this journal: Scientific Publications, 535 N Dearborn St, Chicago, IL 60610.

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For a brief summary of prescribing information, please see following page.

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Indications: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)* — Active immunization against measles (rubeola) in children 15 months of age or older.
BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD) — Simultaneous immunization against rubella and mumps in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling.
MERUVAX®II (Rubella Virus Vaccine, Live, MSD) — Immunization against rubella (German measles) in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling. May be useful for adolescent and adult males to prevent or control rubella outbreaks in circumscribed population groups. In postpubertal females vaccination must not be undertaken unless the woman is not pregnant, is susceptible to rubella (as shown by Hemagglutination Inhibition test), agrees not to become pregnant for next three months (also in immediate postpartum period), and is informed of frequent occurrence of self-limited arthralgia and possible arthritis beginning two to four weeks after vaccination.
M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD) — Simultaneous immunization against measles, mumps, and rubella in children 15 months of age to puberty.
M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD) — Simultaneous immunization against measles (rubeola) and rubella (German measles) in children 15 months of age to puberty.
MUMPSVAX® (Mumps Virus Vaccine, Live, MSD) — Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis; therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic and dysgammaglobulinemic states.

Hypersensitivity to Eggs, Chicken, or Chicken Feathers: For measles- and/or mumps-containing vaccines, in patients hypersensitive to eggs, chicken, or chicken feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions.

Pregnancy: *ATTENUVAX* — The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.
Vaccine administration to postpubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of postpubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception that ATTENUVAX, MUMPSVAX, and/or MERUVAX II may be administered simultaneously. BIAVAX II may be administered simultaneously with ATTENUVAX. Monovalent or trivalent poliovirus vaccine, live, oral, may be administered simultaneously with ATTENUVAX and/or MUMPSVAX. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. However, rubella vaccine may be given prior to discharge to susceptible postpartum patients who received blood products, provided that a repeat HI titer is drawn six to eight weeks after vaccination to insure seroconversion; similarly, although rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness, a follow-up postvaccination HI titer should also be determined.
Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines. Vaccination may not result in seroconversion in 100 percent of susceptible subjects.
Measles-Containing Vaccines — Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.
Rubella-Containing Vaccines — Excretion of live attenuated rubella virus from the nose and throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, is not regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.
Measles-Containing Vaccines — Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who previously received killed measles vaccine; the combination vaccines were not given under this condition in clinical trials.
Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5 to 10 cases of SSPE per million cases of natural measles.
Rubella-Containing Vaccines — Adverse reactions include malaise, sore throat, headache, fever, and rash; mild local reactions such as erythema, local pain, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia that is infrequently associated with signs of inflammation, and polyneuritis.
Moderate fever (101–102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.
Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. In children, joint reactions are rare and of brief duration if they do occur. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3 percent; women: 12–20 percent), and the reactions tend to be more marked and of longer duration. Rarely, symptoms may persist for a matter of months. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (35–45 years), these reactions are generally well tolerated and rarely interfere with normal activities.
Mumps-Containing Vaccines — Parotitis and orchitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2–8 C (35.6–46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2–8 C (35.6–46.4 F), and discard if not used within eight hours. Use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.
Color: The color of the vaccine when reconstituted is yellow. ATTENUVAX is acceptable for use only if clear.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)* — Single-dose vials of lyophilized vaccine, containing when reconstituted not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.
BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.
MERUVAX®II (Rubella Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than the equivalent of 1,000 $TCID_{50}$ of rubella virus vaccine expressed in terms of the assigned titer of the FDA Reference Rubella Virus, and approximately 25 mcg neomycin.
M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin.
M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles and Rubella Viruses, and approximately 25 mcg neomycin.
MUMPSVAX® (Mumps Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.
Each of these vaccines is supplied as a single-dose vial with a disposable syringe containing diluent and fitted with a 25-gauge, 5/8" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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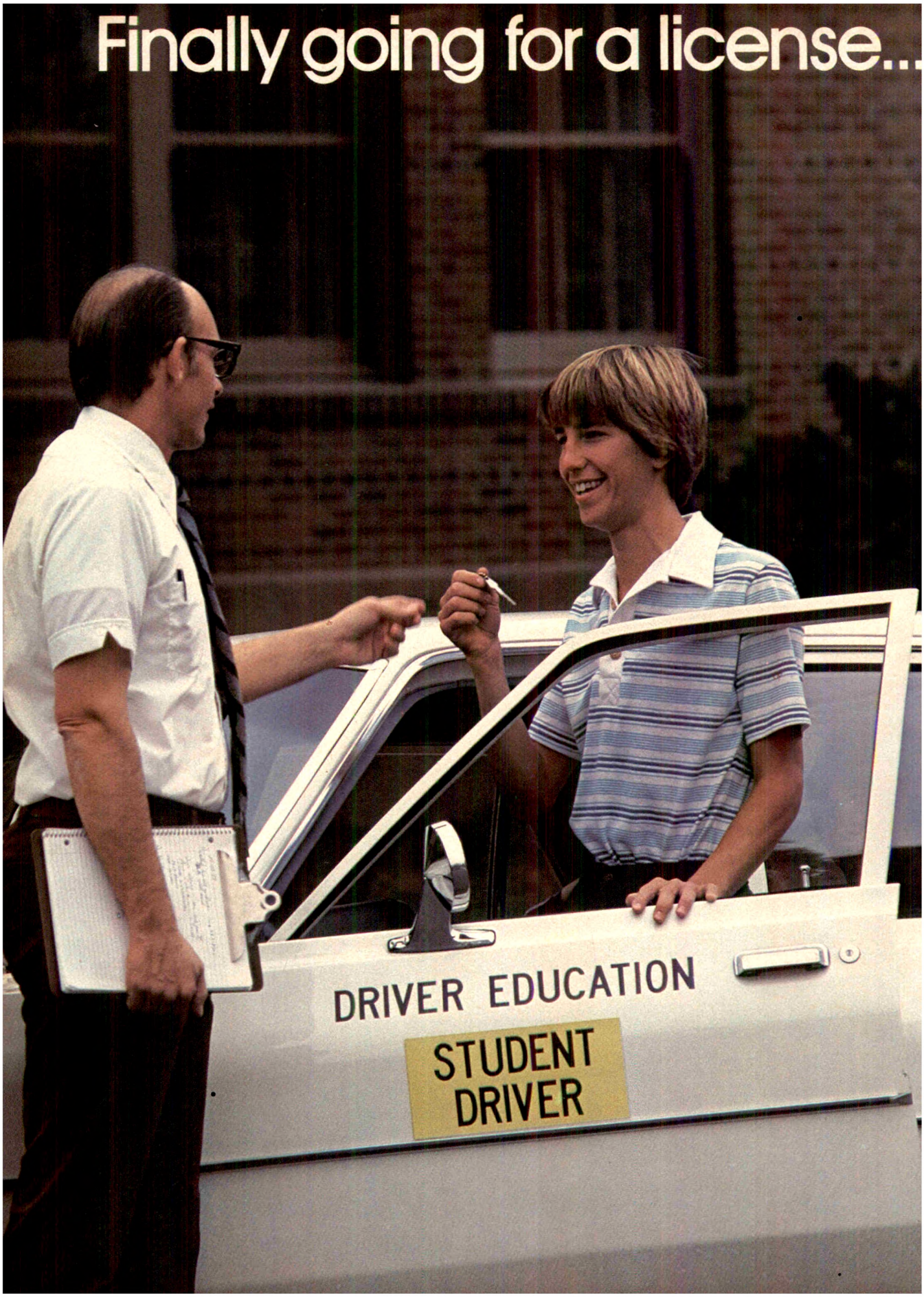
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Valproic Acid

For your patients with mixed seizures including absence, or pure absence

Effective seizure control[1] without cosmetic disfigurement

In 28 studies of patients with mixed grand mal and absence, 76% of all patients gained significant improvement; over one-third became seizure-free. In 60 studies involving pure absence, 86% of patients were improved; half became seizure-free.

While serious side effects, including fatal hepatitis, have occurred, the most common side effect with Depakene is G.I. upset, which usually responds to temporary dosage reduction. Problem sedation is not common and cosmetic stigmata such as gum hypertrophy and hirsutism do not occur.

A widely useful anticonvulsant

Depakene is indicated as sole or adjunctive therapy in both simple and complex absence seizures. It is also indicated for adjunctive treatment of patients with multiple seizure types which include absence. Clinical response has been especially noteworthy among patients with generalized tonic-clonic attacks, or with minor motor seizures (e.g., myoclonic movements, akinetic seizures), where combined with absence.

Offering your patients a chance for a better life

Sustained freedom from seizures can mean a drivers license, an active social schedule, involvement in athletic competition—a better life for your patient.

1. Worldwide studies of Depakene experience (Data refer only to grand mal and/or absence seizures. Since each type was evaluated separately, some patients appear in both groups. Though most of these studies were uncontrolled and had widely differing protocols, their collective data clearly support efficacy of the drug).

See overleaf for prescribing information

Abbott Laboratories,
North Chicago, Illinois 60064

0013326R2

Depakene®
Valproic Acid Capsules 250 mg
250 mg/5 ml syrup

Depakene®
Valproic Acid

Offering a chance for a better life for your patients with mixed seizures including absence, or pure absence

A BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

See WARNINGS for statement regarding fatal hepatic dysfunction.

CONTRAINDICATIONS: DEPAKENE (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidences usually have occurred during the first six months of treatment with DEPAKENE. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy and anorexia. Liver function tests should be performed prior to therapy and at frequent intervals thereafter. Caution should be observed when administering DEPAKENE to patients with pre-existing hepatic disease.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Usage in Pregnancy: THE EFFECTS OF DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTICONVULSANT DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTICONVULSANT DRUGS. THEREFORE, ANTICONVULSANT DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS: *Hepatic dysfunction:* See WARNINGS.

General: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Since DEPAKENE (valproic acid) may interact with concurrently administered anticonvulsant drugs, periodic serum level determinations of concomitant anticonvulsant drugs are recommended during the early course of therapy. (See Drug Interactions).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information For Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NON-RENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF DEPAKENE AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF DEPAKENE AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See ADVERSE REACTIONS).

There have been reports of altered thyroid function tests associated with DEPAKENE. The clinical significance of these is unknown.

Carcinogenesis, Mutagenesis: There has been insufficient study of the drug in animals to determine whether it has carcinogenic potential. Carcinogenicity studies in rats and mice are currently in progress.

Mutagenesis studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Pregnancy: See WARNINGS.

Nursing Mothers: DEPAKENE is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. As a general rule, nursing should not be undertaken while a patient is receiving DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

ADVERSE REACTIONS: Since DEPAKENE (valproic acid) has usually been used with other anticonvulsant drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of othe anticonvulsant medication. Ataxia, headache, nystagmus, diplopi asterixis, "spots before eyes", tremor, dysarthria, dizziness, and incoo dination have rarely been noted. Rare cases of coma have been noted patients receiving valproic acid alone or in conjunction with phenoba bital.

Dermatologic: Transient increases in hair loss have been observe Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, h peractivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic ac inhibits the secondary phase of platelet aggregation. (See DRUG IN TERACTIONS). This may be reflected in altered bleeding time. Bruisin hematoma formation and frank hemorrhage have been reported. Relativ lymphocytosis and hypofibrinogenemia have been noted. Leukopenia an eosinophilia have also been reported.

Hepatic: Increases in serum alkaline phosphatase and elevations serum glutamic oxaloacetic transaminase (SGOT) have been note Elevation of SGOT may be dose related. Elevations of SGPT and LD have been noted less frequently. Isolated cases of severe hepatotoxicit have been reported but do not appear dose related. (See WARNINGS)

Endocrine: There have been reports of irregular menses and secondar amenorrhea occurring in patients receiving DEPAKENE.

Pancreatic: There have been reports of acute pancreatitis occurring patients receiving DEPAKENE.

OVERDOSAGE: Overdosage with valproic acid may result in dee coma.

Since DEPAKENE is absorbed very rapidly, the value of gastric evacua tion will vary with the time since ingestion. General supportive measure should be applied with particular attention being given to the mainte nance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects DEPAKENE overdosage. Because naloxone could theoretically also revers the anticonvulsant effects of DEPAKENE it should be used with caution.

DOSAGE AND ADMINISTRATION: DEPAKENE (valproic acid) administered orally. The recommended initial dose is 15 mg/kg/day, in creasing at one week intervals by 5 to 10 mg/kg/day, until seizures ar controlled or side effects preclude further increases. The maximu recommended dosage is 60 mg/kg/day. If the total daily dose exceed 250 mg, it should be given in a divided regimen.

The following table is a guide for the initial daily dose of DEPAKEN (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 — 24.9	22 — 54.9	250	0	0	1
25 — 39.9	55 — 87.9	500	1	0	1
40 — 59.9	88 — 131.9	750	1	1	1
60 — 74.9	132 — 164.9	1,000	1	1	2
75 — 89.9	165 — 197.9	1,250	2	1	2

The frequency of adverse effects (particularly elevated liver enzymes may increase with increasing dose. Therefore, the benefit gained by in creased seizure control by increased dosage must be weighed against th increased incidence of adverse effects sometimes seen at higher doses

A good correlation has not been established between daily dose, serur level and therapeutic effect, however, therapeutic serum levels for mos patients will range from 50 to 100 mcg/ml. Occasional patients may b controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of pheno barbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administra tion of the drug with food or by slowly building up the dose from an initia low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING T AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED: DEPAKENE (valproic acid) is available a orange-colored soft gelatin capsules of 250 mg valproic acid bottles of 100 capsules (**NDC** 0074-5681-13), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (**NDC** 0074-5682-16).

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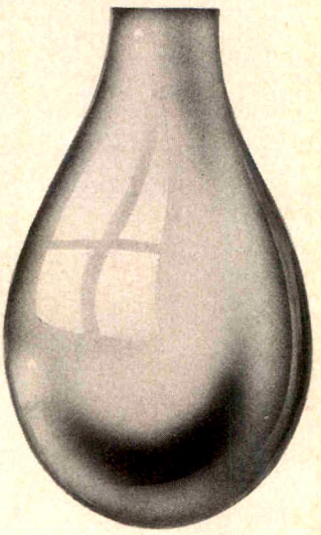
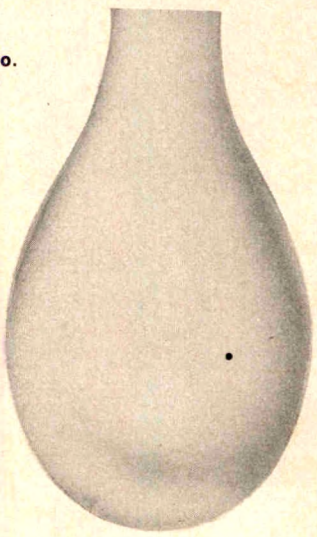


The white suspension



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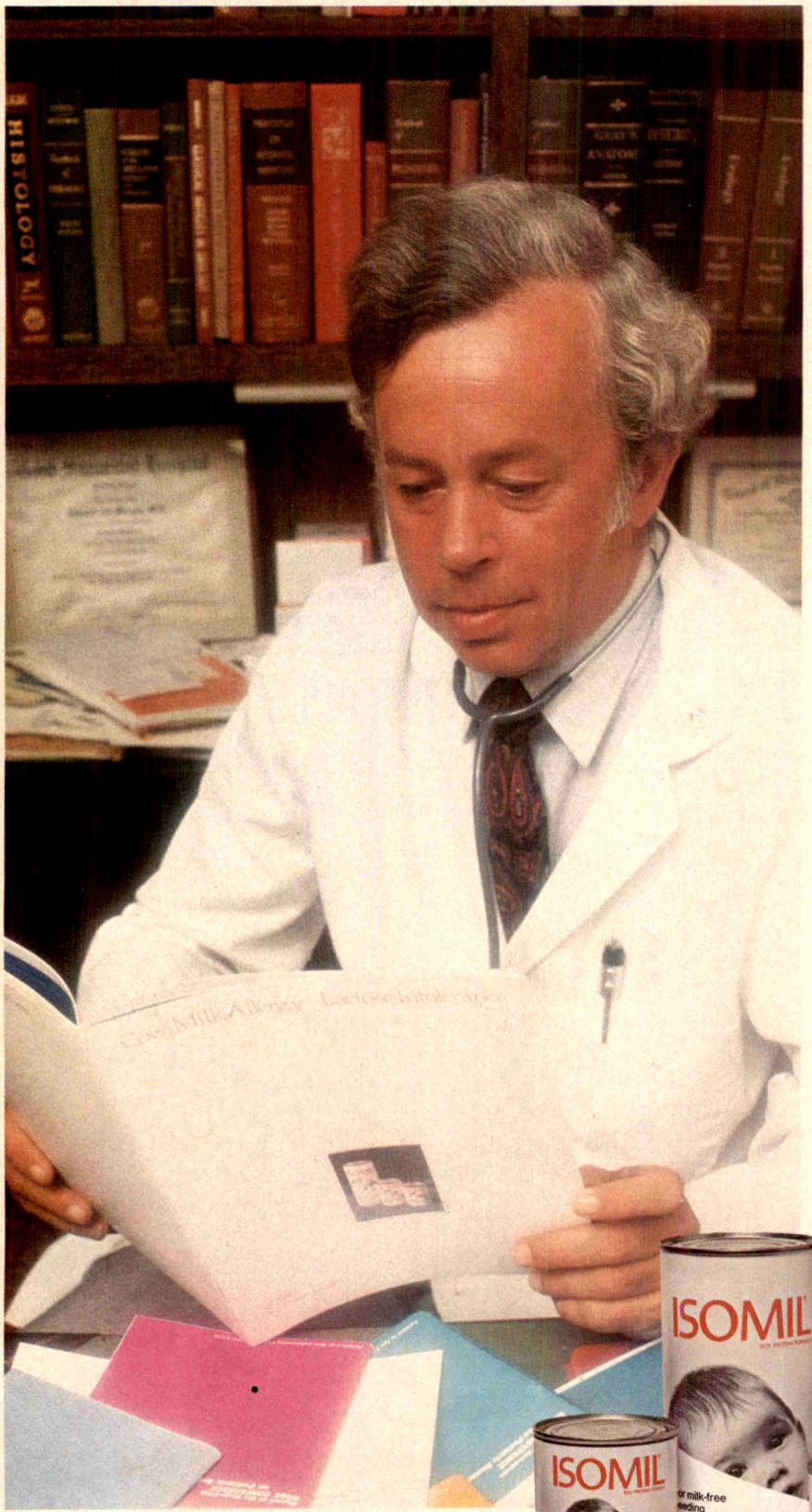

What does a tradition of clinical research mean to you? Simply, it means you can recommend Isomil® Soy Protein Formula with confidence that your patients' nutritional needs will be met. One study, for example, documented that infants will grow as rapidly when fed Isomil as those infants fed a cow milk formula.[1] A second study confirmed these findings.[2]

Isomil was also found effective in preventing recurrence of diarrhea due to secondary lactose intolerance. One clinical study found that diarrhea recurrence rates were lower with the group fed Isomil than those fed a milk-based formula.[3] Another study confirmed these findings.[4]

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References:

1. Dean ME: A study of normal infants fed a soya protein isolate formula. *Med J Aust* 1:1289, 1973.
2. Jung AL, Carr SL: A soy protein formula and a milk-based formula. *Clin Pediatr* 16:982, 1977.
3. Leake RD, Schroeder KC, Benton DA, et al: Soy-based formula in the treatment of infantile diarrhea. *Am J Dis Child* 127:374, 1974.
4. Gabr M, Maraghi S, Morsi S: Management of lactose intolerance secondary to acute diarrhea with a soy-based, lactose-free formula. *Clin Therapeutics* 2:271, 1979.

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Screening of Newborns for Cystic Fibrosis

The report by Berry et al (see p 930) raises the question of mass screening of newborns for cystic fibrosis (CF). The authors suggest that mass screening is advisable, but do not believe enough data are available to recommend the best procedure. Both of these conclusions may be questioned. The advantages of early diagnosis should be examined. Also, since their article reports the examination of 65,000 meconium specimens, and a collaborative study[1] funded by the National Cystic Fibrosis Foundation reports the examination of more than 100,000 specimens, it should be possible at this point to draw some conclusions about the efficacy of various testing procedures.

It is difficult to argue that the early diagnosis of any disease is not in some way beneficial. However, one may vastly overstate the benefit. This seems to have occurred when Berry et al quoted an estimate "that up to 90% of undiagnosed CF patients died during the first two years of life." The reference[2] is not convincing, as it is from an abstract that refers to another abstract[3] (both read by title alone), neither of which presents any data to support this remarkable conclusion.

If it is assumed that most infant deaths of unknown cause are not due to cystic fibrosis (the disease being usually apparent at the time of autopsy), the benefits of early diagnosis would be to the asymptomatic or mildly symptomatic patient. If treatment of these patients is advantageous, it is fair to ask what specific treatment is helpful. Pancreatic enzymes or a predigested formula given to a patient growing normally despite pancreatic insufficiency will decrease the appetite and make the stools more normal. There is little reason to suspect that enzymes alone would lower morbidity or mortality. Mist tent therapy is not useful.[4] Postural drainage and chest physical therapy cannot be expected to benefit greatly the patient who does not have significant pulmonary disease.

If morbidity and mortality are actually lowered by early diagnosis, it is probably because of therapy with antibiotics. It seems possible that such therapy given early in the course of the disease would be beneficial. This, however, is unproved. One wonders if continuous therapy retards the progress of pulmonary disease. Is intermittent therapy for episodes of productive coughing superior to continuous therapy, or to no therapy? Obviously, controlled prospective studies could answer these questions. One must wonder why they have not been done.

Early diagnosis of CF certainly provides the benefit of genetic counseling at an optimal time. Prior to this study, however, Berry et al found that approximately 50% of the patients in their clinic were diagnosed before 18 months of age. In turn, I and my colleagues reviewed the histories of 88 index cases in our clinic, an index case being defined as the first CF patient diagnosed in a family. The conditions of only 35% of these patients were diagnosed during the first year of life. However, many of those cases not diagnosed during the first year were symptomatic during this period. During their first year, 67% of those not diagnosed had abnormal stools, 40% had a continuous cough, and 33% had both. Of the 88 patients, only 17% were asymptomatic during the first year.

The data from the collaborative study of meconium and from the article of Berry et al can be briefly summarized. In the collaborative study, meconium from 102,159 infants was tested with a paper strip test (BMC Test Strip) according to the instructions. There were 216 positive test results, of which 18 were found to have sweat-test-confirmed CF. Five children with negative test results were later found to have CF.

Mass screening with this test was not recommended. The false-positive result rate of 92% necessitates 12 sweat tests to diagnose one CF patient. Since many centers try to avoid doing sweat tests before 6 weeks of age because of the frequency of inadequate sweating in younger infants, considerable parental anxiety would surely occur during the waiting period. There were five known false-negative results, possibly more. Of those tested, 87% were white. An incidence in whites of 1:2,000 is frequently mentioned, though not proved. Using this incidence, one can calculate that 44 CF patients might have been expected, which suggests a false-negative result rate of 59%.

Berry et al used different, and possibly superior, technology. In 20,490 specimens, all subjects with possibly positive paper strip test results were followed up with a more quantitative test for albumin, radial immunodiffusion. In 44,816 subsequent specimens, the same procedure was followed, but only on those specimens initially positive for lactase. The data are presented in a manner that allows separate analysis of whites, whose incidence of CF is high, and normal-birth-weight infants, whose incidence of false-positive results is low.

When the data of Berry et al on white, normal-birth-weight infants is analyzed, the results seem encouraging. The combination of the paper strip test plus radial immunodiffusion brings the false-positive result rate down to 68%. The false-negative result rate, when all specimens were paper strip tested, and again assuming a 1:2,100 incidence, is only 28%.

Preliminary screening for lactase may have missed some CF patients. The data suggest a false-negative result rate of 68%.

Unfortunately, none of this is significantly different ($P < .2$) from the results of the collaborative study. Data from the collaborative study are not presented in a manner that allows separation of whites and normal-birth-weight infants. If such a separation was possible, it might, or might not, be possible to show that the modification of the paper strip test of Berry et al was a significant improvement. Though the use of the test for lactase as an initial screen seems to increase the false-negative result rate, this result is also not statistically significant.

Although Berry et al suggest further studies, some prediction of the probable results of such studies is possible. Specifically, relatively high rates of false-positive and false-negative results would be expected. The cost-to-benefit ratio would be high.

The basic biochemical defect in CF still eludes us. No serum factor has been identified biochemically, and no biological test for a serum factor is sufficiently accurate to allow confident identification of heterozygotes or homozygotes. Some doubt the existence of a serum factor.[5] With funds for health care increasingly limited, an argument can be made for neglecting meconium and concentrating on basic research. While waiting for the results of such research, the clinician interested in CF and its early diagnosis might encourage continuing medical education. As mentioned, only 17% of our patients were completely asymptomatic during their first year of life.

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References

1. Holzclaw DS, Berry HK, Bruns W, et al: Meconium screening for cystic fibrosis: A collaborative study, in *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1977, p 54.
2. Warwick WJ: Ascertainment of CF in Minnesota, in *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1979, p 88.
3. Warwick WJ, Pogue RE: Missing patients with cystic fibrosis, in *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1978, p 99.
4. Motoyama EK, Gibson LE, Zigas CJ: Evaluation of mist tent therapy in cystic fibrosis using maximum expiratory flow volume curve. *Pediatrics* 50:299-306, 1972.
5. Wood RE, di Sant'Agnese PA: Bioassays of cystic fibrosis factor. *Lancet* 2:1452-1453, 1973.

Minimal Brain Dysfunction and Hyperkinesis

A Clinical Viewpoint

During the last 20 years much attention has been given in the medical and psychological literature to the syndrome of minimal brain dysfunction (MBD) or hyperkinesis (hyperactivity), the terms generally being used interchangeably. Experts have emphasized the high frequency and clinical importance of this condition and have warned clinicians about the necessity of early detection and proper treatment. The conscientious clinician cannot fail to be impressed by the magnitude of this literature and its sense of urgency.

However, when the clinician inspects these reports closely, the concept is found to be so poorly described that deciding whether a particular case fits the definition adequately is difficult. The expert consultant, who is presented with a child with clear evidence of academic or behavioral problems, may label such a case as MBD with little hesitation, but the primary care clinician is often perplexed.

The purposes of this communication are to review critically the recent literature to establish the extent of this uncertainty of definition of MBD and the consequences of this situation and to suggest a solution.

REVIEW OF THE LITERATURE

The extensive literature on MBD can be organized under several headings for review and analysis.

Original Definition

In an effort to update the work of Strauss and Lehtinen,[1] a US Public Health Service task force, under the leadership of Clements, met and published in 1966 a monograph[2] in which they attempted to clarify the mounting confusion by standardizing terminology and providing a definition of

MBD. The committee's definition is as follows:

> Children of near average, average, or above average general intelligence with certain learning or behavioral disabilities ranging from mild to severe, which are associated with deviations of function of the central nervous system. These disabilities may manifest themselves by various combinations of impairment in perception, conceptualization, language, memory and control of attention, impulse, or motor function.

The statement goes on to list a considerable variety of behavioral, cognitive, and neurological findings, which may accompany the syndrome. A striking omission is any mention of the minimum criteria that must be fulfilled to allow the diagnosis to be applied with certainty.

Little help came from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-II).*[3] Their definition offered for the hyperkinetic reaction of childhood is as follows:

> This disorder is characterized by overactivity, restlessness, distractibility, and short attention span, especially in young children; the behavior usually diminishes in adolescence.

Once again no delineation of these characteristics and no set criteria necessary for the diagnosis were offered to the clinician. In the *DSM-III*, to be published in 1980,[4] the hyperkinetic reaction is renamed an "attention deficit disorder." Although the description has now been expanded from three lines to four pages, it fails to achieve necessary clarity, as we shall point out later.

Differentiation of MBD From Normal

A syndrome is usually thought of as a group of abnormal signs and symptoms characterizing a disease state, such as the sore throat, fever, and positive throat culture that define a streptococcal pharyngitis. It is difficult to understand, therefore, how the behavioral syndrome said to characterize MBD can be diagnosed, since not one of the experts writing about MBD has instructed us as to where the normal leaves off and the abnormal begins. The traits of high activity, high distractibility, and low persistence (or attention span) are temperamental characteristics that have been demonstrated by Thomas et al[5,6] to exist in the general population and are found in children who do not have problems in school adjustment.[7] If 50% of the population is by definition more active than the mean, how active must a child be to be labelled as hyperactive or hyperkinetic? How is this to be measured and by whom? If it is not the quantity of the activity but the quality, what is that quality that is the real problem?

Furthermore, not only are the behaviors in the MBD syndrome poorly differentiated from normal characteristics, but some of the other components of the syndrome are considered abnormal only because they are found at later than the expected ages, such as the various disabilities in information processing and the neurological "soft signs." What are the precise ages when, for example, not reading well or certain sorts of clumsiness become evidence for brain dysfunction? In other words, unlike the usual criteria for a syndrome, the characteristics of MBD are altered by maturation.

Definition Used in Current Research

The vagueness in the original definition of MBD and the failure of its proponents to differentiate the syndrome adequately from the normal seem to be responsible for confusion in both research and practice. The bewildered clinician, looking for some clarification as to what is being diagnosed as MBD by the experts, might expect enlightenment while perusing research papers. Our training has taught us that subjects under scientific study should be meticulously defined.

However, this quest will disappoint the clinician. In some cases the subjects are merely described as "hyperactive,"[8,9] as if this term were universally understood. In other studies the children described have been referred by other physicians with the diagnosis already made on criteria that are not revealed.[10,11] Some investigators simply say that the diagnosis was made in a previous study.[12,13] Connors' parent and teacher questionnaires[14] have been used as the means of diagnosis in many investigations although this technique may suffer from the major weakness of subjectivity. The mother or teacher is asked for general judgments as to whether the child is "restless or overactive," "excitable" etc or not. These global perceptions are given numerical scores and treated as if they were objective data.

This confusion as to who may be the subjects of these studies not only leaves ungratified our search for a definition of MBD but also makes the results of almost all these studies uninterpretable.

Criteria Used in Clinical Practice

If academicians and researchers have been so lacking in precision about the phenomena under study, we should hardly expect practitioners to be doing any better. Indeed, that seems to be the case.

Variations in reported frequencies of MBD or hyperactivity are probably a reflection of these multiple standards of diagnosis. Kenny et al[15] found that only a quarter of the children referred by practitioners to their diagnostic center for hyperactivity were actually overactive. Lambert et al[16] showed that the frequency of hyperactivity ranged from 1% to 13%, depending on who was defining it: parents, teachers, physicians, investigators, or some combination of these. Johnson and Prinz[17] concluded that hyperactivity is "in the eye of the beholder."

Sandoval et al[18] studied the criteria used for diagnosing hyperactivity in the Oakland, Calif, region and found that the prevailing practice was to rely primarily on behavioral descriptions from parents and little on observed behavior or other objective findings.

In considering the vague definitions and applications of the diagnostic terms, it is not surprising that there is a real problem in determining whether the elimination diet proposed by Feingold for "hyperactivity" has any therapeutic value.[19]

Consequences of Present Practice

The diagnostic confusion in the area of MBD and hyperactivity has led to

unfavorable consequences for children, their parents, and the professional persons who are trying to help them. The poor prognosis is evidence that current efforts are not working.

Children seem to be the ones to suffer the most, since even the best of present treatment of this ill-defined condition is far from satisfactory.[20] One major obstacle to suitable management is the uncertainty as to who has and who does not have the syndrome. One can only speculate as to the amount of iatrogenic pseudodisease[21] flourishing today as numerous neurologically intact children and their parents are informed that something is wrong with the child's brain. Once the label is applied to the child, the clinician must select from a variety of available therapeutic modalities: psychological, medical, educational, and dietary, none of which seems clearly superior to the others. The question about use of cerebral stimulants has been further clouded by the discovery that the behavioral changes induced by treatment (decreased activity and improved performance on cognitive tests), which were once thought to be specific and diagnostic of MBD, have also been demonstrated in normal children.[22] In a recent review of the literature Barclay[20] concluded that

> ... our current treatment approaches do not, as yet, appear to alter the prognosis of the disorder, as promising as they may be in the short-term manageability of these children.

This gloomy outlook is shared by authors of other recent reviews.[23-25]

Although children clearly are the ones most adversely affected by the diagnostic confusion over MBD, there are others who are deeply touched by it. As many clinicians know, parents are perplexed about the diagnosis and treatment of MBD or hyperactivity, since they are given conflicting advice by professional persons. However, the physicians, psychologists, and educators are laboring under the same disadvantage. To be a responsible clinician in the present setting is a formidable task. Finally, the research that should be showing us the way out of this quandry is largely trapped in the quagmire of diagnostic vagueness, as has been described above.

A WAY OUT OF CONFUSION

There seem to be only two ways out of the present diagnostic and therapeutic confusion. We must establish clear, objective criteria for these diagnoses or else we must discard them. If the terms are to be abandoned, some new diagnostic scheme must be developed to describe adequately the great variety of problems now grouped together under these labels.

In redefining hyperactivity as an attention deficit disorder,[4] the authors of the *DSM-III* seem to recognize the fact that for children having trouble adjusting to school, it is not the activity that is the main obstacle. However, although the *DSM-III* proposes six criteria for the syndrome between the ages of 8 and 10 years, it does not say how many of the criteria must be met, what is meant by such global diagnostic descriptions as "easily distracted" or "moves excessively during sleep," or exactly how the definition applies to other ages.

Those who believe that the terms are useful and who wish to retain them might look to the example of how Jones'[26] brought order out of diagnostic confusion over rheumatic fever in 1944. After his report it was no longer possible to say that any child with fever and joint pains had rheumatic fever. The physician was required to demonstrate two major or one major and two minor signs of the disease supported by evidence of recent streptococcal infection. All of these manifestations are objective findings (with the exception of the arthralgia, one of the minor ones) and none is based on hearsay evidence.

If MBD and hyperactivity were a coherent syndrome based on objective findings, such an approach would offer a real promise. However, there is a growing body of expert opinion from several disciplines that the syndrome is too diffuse and too subjective for such objective definition. These criticisms are based on several deficiencies noted in a variety of settings. In reviewing the literature on brain damage syndromes in childhood, Rutter[27] concluded that "the behavioral stereotype of the brain damaged child must be firmly rejected." Sandberg et al,[28] from a study of psychiatric clinic patients, decided that "there was no evidence for the validity of a broad concept of hyperkinetic syndrome." Shaffer and Greenhill[29] found that the diagnosis

> ... tells little about aetiology and does not permit generalizations to be made about clinical state. Its usefulness in predicting response to drug or other forms of treatment has yet to be demonstrated.

Schmitt[30] agreed, calling MBD a "myth." Saravia-Campos[31] believed it is an oversimplification and called for a return to the complexities of children as they really are. Ingram[32] said that MBD "is not a diagnosis; it is an escape from making one."

Our own research experience places us firmly in agreement with these views. In a recent study[33] of 60 children, referred to a pediatric neurologist by schools and physicians for problems in behavior and learning, data were collected on behavioral characteristics, cognitive or perceptual difficulties, and neurological soft signs. A reanalysis of those data showed that anywhere from 15% to 90% of this group could be given the diagnosis of MBD, depending on how the current diagnostic criteria were applied. One cannot fail to be impressed that for 75% of this referred population, the clinician's own interpretation of the existing diagnostic criteria could determine the diagnosis.

Since it appears unlikely that MBD and hyperactivity can be diagnosed on the basis of clear, objective criteria, it is our belief that the terms should be abandoned. Papers presented to our professional journals without meticulous description of the subjects being studied should be unconditionally rejected.

It is not sufficient, however, to deprecate the inadequacies of the current terminology of MBD and hyperactivity. Some clearer and more objective diagnostic scheme must be used in its place. We propose that problems in behavior and learning in children be diagnosed in terms of a neurobehavioral profile. Such a profile could consist in a summary of objective evi-

dence under six headings: (1) general physical status, including growth; (2) neurological status based on examination findings as to motor function, reflexes, coordination, including "soft signs," and sensation, including vision and hearing; (3) information-processing abilities; (4) maturation; both psychomotor, including speech, and cognitive; (5) temperament or behavioral style, in particular adaptability, attention span, and activity; and (6) psychosocial adjustment, including evidence of social cooperation, autonomy, aggressiveness, and withdrawal. Added to every neurobehavioral profile must be a description of the child's living situation, that is, the environmental input and interaction. If the child is viewed by parents or teachers as abnormal in any respect, the person complaining should be identified and the nature of the interactional difficulty described adequately. The profile would include strengths as well as disabilities and would always be subject to revision.

The neurobehavioral profile would replace vague general diagnoses with a summary of more objective data. Findings in one area, such as temperament or information processing, would not lead to unsupported conclusions in others, such as neurological status. The question of the importance of neurological soft signs[32-37] would be avoided by simply stating under the heading of neurological status what findings were present.

Three main purposes would thereby be served: (1) In clinical practice there would be a greater assurance that all pertinent factors would be considered in diagnosis and would be included in professional communications. Plans for therapy or special education based on detailed diagnostic profiles rather than stereotypic labels would have a greater chance of successfully meeting the needs of individual children. (2) In research there would be a more precise definition of subjects. Instead of calling a child simply "hyperactive," the researcher would be obliged not only to describe the child's activity but also to consider all the other pertinent aspects of the case. (3) In education it would be possible to encourage both teachers and students to think of children in their true complexity and avoid facile general diagnoses based on inadequate data.

It is likely that clinical syndromes based on more objective data from such a profile will emerge and will prove useful in clinical management of problems in behavior and learning in children. Such syndromes, however, would have the advantage of being clearly derived from more objective data and being unencumbered by vague terminology. It will take a great deal of effort to get to that point from where we are today, but our children deserve no less.

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References

1. Strauss AA, Lehtinen L: *Psychopathology and Education of the Brain Injured Child*. New York, Grune & Stratton Inc, 1947.
2. Clements SD: *Minimal Brain Dysfunction in Children*. Washington, DC, Dept of Health, Education, and Welfare, 1966.
3. *DSM-II: Diagnostic and Statistical Manual of Mental Disorders*, ed 2. Washington, DC, American Psychiatric Association, 1968.
4. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*, ed 3. Washington, DC, American Psychiatric Association, to be published.
5. Thomas A, Chess S, Birch HG, et al: *Behavioral Individuality in Early Childhood*. New York, New York University Press, 1963.
6. Thomas A, Chess S, Birch HG: *Temperament and Behavior Disorders in Children*. New York, New York University Press, 1968.
7. Carey WB, Fox M, McDevitt SC: Temperament as a factor in early school adjustment. *Pediatrics* 60(suppl):621-624, 1977.
8. Bugental DB, Collins S, Collins L, et al: Attributional and behavioral changes following two behavior management interventions with hyperactive boys: A follow-up study. *Child Dev* 49:247-250, 1978.
9. Swanson JM, Kinsbourne M: Stimulant-related state-dependent learning in hyperactive children. *Science* 192:1354-1357, 1976.
10. Firestone P, Peters S, Rivier M, et al: Minor physical anomalies in hyperactive, retarded and normal children and their families. *J Child Psychol Psychiatr* 19:155-160, 1978.
11. O'Leary SG, Pelham WE: Behavior therapy and withdrawal of stimulant medication in hyperactive children. *Pediatrics* 61:211-217, 1978.
12. Dalby JT, Kinsbourne M, Swanson JM, et al: Hyperactive children's underuse of learning time: Correction by stimulant treatment. *Child Dev* 48:1448-1453, 1977.
13. Harley JP, Matthews CG, Eichman P: Synthetic food colors and hyperactivity in children: A double-blind challenge experiment. *Pediatrics* 62:975-983, 1978.
14. Connors CK: A teacher rating scale for use in drug studies with children. *Am J Psychiatr* 126:884-888, 1969.
15. Kenny TJ, Clemmens RL, Hudson BW, et al: Characteristics of children referred because of hyperactivity. *J Pediatr* 79:618-622, 1971.
16. Lambert NM, Sandoval J, Sassone D: Prevalence of hyperactivity in elementary schoolchildren as a function of social system definers. *Am J Orthopsychiatr* 48:446-463, 1978.
17. Johnson CF, Prinz R: Hyperactivity is in the eyes of the beholder. *Clin Pediatr* 15:222-238, 1976.
18. Sandoval J, Lambert NM, Yandell W: Current medical practice and hyperactive children. *Am J Orthopsychiatr* 46:323-334, 1976.
19. Wender E: Food additives and hyperkinesis. *Am J Dis Child* 131:1204-1206, 1977.
20. Barclay RA: Recent developments in research on hyperactive children. *J Pediatr Psychol* 3:158-163, 1978.
21. Carey WB, Sibinga MS: Avoiding pediatric pathogenesis in the management of acute minor illness. *Pediatrics* 49:553-562, 1972.
22. Rapoport JL, Buchsbaum MS, Zahn TP, et al: Dextroamphetamine: Cognitive and behavioral effects in normal prepubertal boys. *Science* 199:560-563, 1978.
23. Weiss G, Hechtman L, Perlman T: Hyperactives as young adults: School, employer and self-rating scales obtained during ten-year follow-up evaluation. *Am J Orthopsychiatr* 48:438-445, 1978.
24. Eisenberg L: Hyperkinesis revisited. *Pediatrics* 61:319-321, 1978.
25. Riddle KD, Rapoport JL: A two-year follow-up of 72 hyperactive boys: Classroom behavior and peer acceptance. *J Nerv Ment Dis* 162:126-134, 1976.
26. Jones TD: Diagnosis of rheumatic fever. *JAMA* 126:481, 1944.
27. Rutter M: Brain damage syndromes in childhood: Concepts and findings. *J Child Psychol Psychiatr* 18:1-21, 1977.
28. Sandberg ST, Rutter M, Taylor E: Hyperkinetic disorder in psychiatric clinic attenders. *Dev Med Child Neurol* 20:279-299, 1978.
29. Shaffer D, Greenhill L: A critical note on the predictive validity of 'the hyperkinetic syndrome.' *J Child Psychol Psychiatr* 20:61-72, 1979.
30. Schmitt BD: The minimal brain dysfunction myth. *Am J Dis Child* 129:1313-1318, 1975.
31. Saravia-Campos J: 'Minimal brain dysfunction': An oversimplification? *Dev Med Child Neurol* 18:246-248, 1976.
32. Ingram TTS: Soft signs. *Dev Med Child Neurol* 15:527-530, 1973.
33. Carey WB, McDevitt SC, Baker D: Differentiating minimal brain dysfunction and temperament. *Dev Med Child Neurol* 21:765-772, 1979.
34. McMahon S, Greenberg LM: Serial neurologic examination of hyperactive children. *Pediatrics* 59:584-587, 1977.
35. Shaffer D: 'Soft' neurological signs and later psychiatric disorder: A review. *J Child Psychol Psychiatr* 19:63-65, 1978.
36. Touwen BCL, Sporrel T: Soft signs and MBD. *Dev Med Child Neurol* 21:528-529, 1979.
37. Barlow CF: 'Soft signs' in children with learning disorders. *Am J Dis Child* 128:605-606, 1974.

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Articles

Elevated Meconium Lactase Activity

Its Use as a Screening Test for Cystic Fibrosis

Helen K. Berry, MA; Frank W. Kellogg, MD; Shirley R. Lichstein; Robert L. Ingberg, MD

• Screening of newborn infants could provide information needed to evaluate the effects of early treatment on the course and prognosis of cystic fibrosis (CF). Two procedures of screening meconium for CF were compared: increased albumin levels, detected by a commercial test strip; and increased lactase activity, detected by glucose production after incubation of meconium with lactose. Specimens positive by the lactase test were retested for albumin. Low-birth-weight infants accounted for more than half the positive test results with both procedures. Sweat chloride measurements were carried out only on infants whose meconium specimens had albumin concentration greater than 12 mg/g (wet weight), measured by radial immunodiffusion. Twelve infants with CF were identified through screening, six while testing 44,816 specimens by lactase activity test. Three additional infants with CF were missed because meconium specimens were negative to both tests.

(*Am J Dis Child* 134:930-934, 1980)

A number of studies have demonstrated raised levels of protein, predominantly of albumin, in meconium from infants with cystic fibrosis (CF).[1-3] On the basis of these studies, a reagent paper strip was developed that contains an indicator to detect increased albumin concentration (BMC Test Strip). This test is widely used in Western European countries.[4,5] In a one-year cooperative screening study in the United States, it was found that modifications of the test were needed before it could be recommended for mass screening. Problems centered around both false-positive and false-negative test results.[6]

For editorial comment, see p 925.

For the period of March 1975 through November 1976, the paper strip test was used to screen meconium specimens for increased albumin levels. Antonowicz et al[7] reported increased disaccharidase activity in meconium from infants with CF and suggested that measurement of lactase activity might be used as an alternative method for the detection of CF. We evaluated detection of raised lactase activity as a screening procedure in a period of from December 1976 through October 1979. During a period of from April 1976 through November 1976, both procedures were carried out, and we have compared results from them.

MATERIALS AND METHODS

Collection and Handling of Specimens

Six hospitals in the Cincinnati area participated in the screening program. The first meconium specimen available after the infant was transferred to the newborn nursery was collected, to avoid contamination with blood in the delivery room. Specimens were placed in clear plastic bags, 5.0 × 7.5 cm, labeled with name, sex, race, birth weight, and hospital identification, and then frozen. Approximately twice weekly, frozen meconium specimens were collected, thawed, and tested. Immediately afterward, specimens were refrozen and stored.

Testing by Paper Strip Test

A small amount of meconium was placed on the bottom of the test strip, which contained a dye (tetrabromophenolphthalein ethyl ester). The strip was inserted into a small glass tube that contained a few drops of water. Albumin was chromatographed in the dye-impregnated paper, and turned a distinctive blue in a positive test. All specimens that showed any color were designated as "screening positive," and quantitative measurements of albumin were carried out.

Detection of Lactase Activity

A small amount of meconium (approximately 10 to 20 mg) was placed in a 13 × 75-mm test tube. Then 0.5 mL of 3% lactose solution in 0.1M maleate buffer, at a pH of 5.4, was added, thoroughly mixed, and allowed to incubate for one hour at room temperature. At the end of the incubation period lactase activity was detected by the presence of glucose, demonstrated by a test stick (Clinstix, Ames Co, Elkhart, Ind). The minimum concentration of glucose required to give a positive test was 0.1 mg/mL. This would correspond to lactase

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activity of 2 to 4 μmole/min/g of protein, if 10 to 20 mg of meconium was tested. All specimens with apparent lactase activity were tested for the presence of free glucose. Only occasional specimens showed free glucose prior to incubation with lactose. All specimens with tests positive for glucose were retested with the paper strip test for albumin. Quantitative albumin measurements were carried out on all specimens that were both lactase-test and glucose-test positive.

Quantitative Measurement of Albumin

Albumin was measured using commercially prepared radial immunodiffusion plates (M-Partigen Albumin, Behring Diagnostics, American Hoechst Corp, Somerville, NJ). An aliquot of meconium was weighed, combined with 9 v/v of water, and mixed thoroughly, followed by sonication. The supernatant after centrifugation was used for albumin determination. Albumin standards were prepared as directed by the manufacturer and used to construct a calibration curve. An aliquot of 5 μL of the supernatant was used. The assay range for albumin using these plates is 44 to 610 mg/dL, corresponding to a range of 4.4 to 61.0 mg/g of meconium (wet weight). Supernatants were diluted if necessary to extend the range upward. Values below 4.4 mg/g were estimated.

Proteolytic Activity by Gelatin Liquefaction

Beginning in 1977, specimens with albumin concentrations greater than 12 mg/g were tested for proteolytic activity as described by Westler and Neal.[8] Specimens from CF infants identified prior to 1977 were also taken from storage and tested if enough samples were left. Approximately 10 to 20 mg of meconium was suspended in 0.5 mL of tris chloride buffer, at a pH of 8.0, containing 0.05M calcium chloride solution and 0.02% sodium azide. An aliquot of 0.5 mL of 7.5% gelatin in tris buffer at a pH of 8.0 was added and the mixture thoroughly shaken. Incubation was carried out in a shaking water bath at 37 °C for one hour. The incubation mixtures were then refrigerated for several hours or overnight. Specimens containing less than 10 μg of trypsin per gram of meconium remained solid, whereas those with higher levels of proteolytic activity were liquefied.

RESULTS

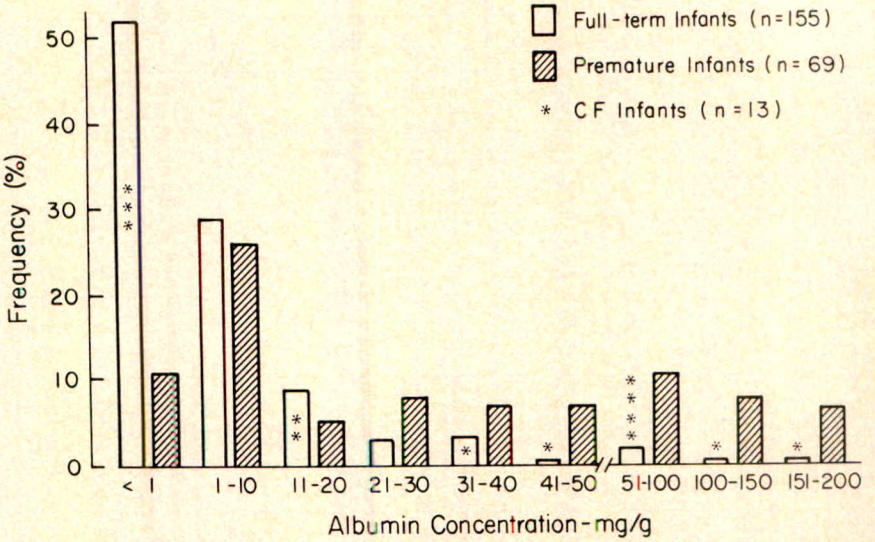
The results of screening 20,490 specimens by paper strip test and 44,816 by lactase are given in Table 1. Comparison of the number of meconium specimens received with the number of infants born in a given year suggested that 98% of the infants were tested. Before screening for lactase was begun on a routine basis to replace the paper strip test, 100 specimens that were positive were retested for lactase activity. Twenty were positive on the lactase test. Specimens from five CF infants, identified by the paper strip test with positive sweat chloride tests, were among those positive on the lactase test. Then, approximately 8,000 specimens were tested by both procedures. Among 41 specimens positive on the paper strip test, 24 were also lactase-test positive. One infant with CF was identified during this period; the meconium was positive on both the paper strip and lactase tests. We believed these preliminary results justified the use of meconium lactase activity as a primary screening procedure.

There were relatively few positive tests using the paper strip test for primary screening, namely 138 or 0.67%. However, when lactase was used as the primary screening method, 3,957 (8.8%) of the specimens gave positive test results. Among the specimens positive on the lactase test, 98 gave positive test results with the paper strip test and were tested for albumin by immunodiffusion.

Table 1.—Comparison of Two Methods for Screening Meconium Specimens

	No. of Specimens Tested	Positive Screening Test, No./%	Albumin level > 12 mg/g, No./%	Positive Sweat Chloride Test, No./%
Paper strip test*				
White	16,958	106/0.62	26/24.5	6/5.7
Black	3,415	31/0.91	5/16.1	0/0
Other	117	1/0.85	0/0	0/0
Total	**20,490**	**138**/0.67	**31**/22.5	**6**/4.3
Lactase Test				
White	37,873	3,083/8.1	45/1.46	6/0.19
Black	6,662	825/12.4	8/0.97	0/0
Other	281	29/10.3	0/0	0/0
Total	**44,816**	**3,937**/8.8	**53**/1.35	**6**/0.15

*BMC Strip Test for albumin.



Albumin concentration in meconium specimens from full-term and premature infants (birth weight < 2,240 g) compared with infants with cystic fibrosis (CF) (all full-term).

Table 2.—Relation of Birth Weight to Test Results

	Specimens Tested		Screening Test Positive		Albumin, > 12 mg/g		Sweat Chloride Test Positive	
	Total	Low Birth Weight,* No./%	Total	Low Birth Weight, No./%	Total	Low Birth Weight, No./%	Total	Low Birth Weight, No.
Paper strip test†								
White	16,958	378/2.2	106	31/29.2	26	14/53.8	6	0
Black	3,415	133/3.9	31	4/12.9	5	3/60.0	0	0
Other	117	0/0	1	0/0	0	0/0	0	0
Total	**20,490**	**511**/2.5	**138**	**35**/25.4	**31**	**17**/54.8	**6**	**0**
Lactase test								
White	37,873	739/2.0	3,083	114/3.7	45	19/42.2	6	0
Black	6,662	261/3.9	825	37/4.4	8	6/75	0	0
Other	281	5/1.8	29	2/6.9	0	0/0	0	0
Total	**44,816**	**1,005**/2.2	**3,937**	**153**/3.9	**53**	**25**/47.2	**6**	0

*Less than 2,240 g. Twins are included.
†BMC Strip Test for albumin.

Table 3.—Infants with Positive Sweat Chloride Tests, 1975 to 1979*

Patient	Family History	Birth Weight, g	Sex/Race	Albumin, mg/g	Proteolytic Activity†	Sweat Chloride Weight, mg	Sweat Chloride Level, mEq/L
Paper strip test‡							
1	+	2,270	F/W	300	A	659	93
2	—	3,150	F/W	19	B	182	123
						452	71
3	+	3,689	M/W	34	B	40	145
						211	112
4	—	3,092	M/W	41	A	84	126
						212	104
5	—	2,810	M/W	67	A	74	140
						133	103
6	+	3,491	M/W	< 2.0	C	152	115
						149	132
7	—	3,008	M/W	15	B	420	107
Lactase test							
8	—	3,689	M/W	115	A	292	108
						98	129
9	—	2,284	F/W	78	A	389	102
10	—	3,319	F/W	55	A	138	116
11§	—	4,200	M/W	56	A	140	98
12	—	2,894	F/W	< 2.0	C	386	94
13	+	3,745	F/W	< 2.0	C	446	103
14	—	3,972	F/W	115	A	67	131
15	—	2,815	F/W	125	A	107	120
						100	114

*Includes three infants with albumin levels less than 2 mg/g who were missed by meconium testing.
†A indicates gelatin solid after incubation, and no proteolytic activity with trypsin level less than 5 μg/g; B, no specimen left; C, gelatin liquefied; proteolytic activity present.
‡BMC Strip Test for albumin.
§Infant had meconium ileus.

The Figure shows albumin content of specimens that gave positive reactions with the paper strip test, either as the primary screening test or after the finding of increased lactase activity. Eighty percent of specimens positive on the paper strip test from low-birth-weight infants had albumin content less than 10 mg/g. Albumin content of greater than 12 mg/g (wet weight) was arbitrarily chosen as the cut-off point, above which sweat chloride measurements would be carried out. The number of specimens containing albumin concentrations of greater than 12 mg/g was similar with both screening procedures, 0.15% and 0.12% (Table 1), so that one infant in 666, compared with one in 833, was recalled for sweat chloride determinations.

Data on the relation of birth weight to test results are given in Table 2. The incidence of premature or small-for-date births was 2% in whites and 4% in blacks. In the initial phase of screening by paper strip test, low-birth-weight infants accounted for a high proportion of specimens with albumin content greater than 12 mg/g (55%). The incidence of low birth weight was slightly higher among infants with lactase-positive tests (3.9%) than in the total population tested (2.2%). Low-birth-weight infants accounted for 47% of the infants with specimens positive on lactase and albumin tests.

Table 3 gives data on family history, birth weight, sex, race, albumin content, proteolytic activity, and sweat chloride measurements of infants identified as having CF during the period of March 1975 to October 1979. Only infants born in participating hospitals were included in the study. Infants from high-risk families were included only if they would have been tested in the course of routine screening. In most instances, sweat chloride determinations were carried out at 4 to 6 weeks of age and again after 6 months of age. We were unaware of the family history in patients 1 and 3 prior to screening and learned of it only after reporting the positive results to the private physi-

cian. Two infants born in participating hospitals were tested for sweat chloride because of a positive family history, in spite of negative meconium tests (patients 6 and 13). Infant 12 had sweat chloride measurement because of recurring pneumonia during the first months of life. Only one infant had meconium ileus. All infants with CF were white and full-term. Sixteen percent of the infants tested were nonwhite. No black infants with CF were found among 10,077 whose specimens were tested. The incidence of CF among blacks is thought to be about one tenth that in whites.

Among babies tested first by paper strip test, the incidence of CF identified as a consequence of screening was six in 20,490 (1:3,400). Of those tested, 16,580 infants were white and full-term. As noted previously, one additional infant with CF (patient 6) was identified during this period because of a positive family history, for a combined total of seven infants with CF (1:2,400) among white, full-term infants tested. This brings the incidence close to the reported incidence in whites of 1:2,000.

Among babies tested first by lactase test, the incidence of CF identified through screening was six in 44,816 (1:7,500). Two infants with CF were not identified by meconium screening (patients 12 and 13), bringing the total number identified in this group to eight. These eight infants with CF were found while testing 37,134 white, full-term infants, for overall incidence during the period when lactase screening was carried out of 1:4,600, approximately half the anticipated incidence. It was expected that 15% to 25% of infants with CF would have normal pancreatic activity and would be missed by a screening test based on elevated albumin levels. It was, therefore, not surprising that three of 15 infants with CF were missed by meconium screening.

Meconium specimens from the three missed infants with CF had been recorded as negative on initial screening. They were taken from storage and retested. All were negative on second testing to paper strip, lactase, and quantitative measurement of albumin tests. Gelatin liquefaction as a test for proteolytic activity was applied to these three specimens, as well as a number of stored specimens positive on albumin test. As noted in Table 3, specimens from identified patients with CF had low or absent proteolytic activity, judged by their failure to liquefy gelatin, whereas specimens from the three infants with CF missed by screening had normal proteolytic activity. The majority of albumin test-positive specimens from premature and low-birth-weight infants readily liquefied gelatin in vitro, in spite of failure of digestion of albumin in vivo.

COMMENT

Attention has recently turned to the importance of early diagnosis for patients with CF. Shwachman et al noted the accumulation of evidence that early diagnosis and treatment affect morbidity and mortality from the disease.[9] Warwick estimated that up to 90% of undiagnosed patients with CF died during the first two years of life.[10] Lubin and Bonner found that of infants with CF diagnosed after 6 months of age, a larger proportion were below the 25th percentile for height and weight, than of those diagnosed before 6 months of age.[11] Palmer et al reported that early diagnosis and treatment was associated with a reduced number of hospital admissions, enhanced growth, and improved clinical condition.[12]

Screening for CF in infants could provide information needed to evaluate the effect of early treatment on the course and prognosis of the disease. The cost of screening might be recovered by recognition of CF in an infant prior to development of symptoms, thus avoiding costly hospitalizations for diagnosis. Screening for a genetic disease such as CF means that families recognize the presence of the disorder early and can make better decisions regarding future family planning.

Tests based on increased amounts of total protein or of individual proteins in meconium offer the best prospect as a screening procedure at present. The Cystic Fibrosis Foundation sponsored a collaborative study by four CF centers to evaluate the paper strip test as a means of detecting raised albumin levels in meconium.[6] Two additional centers, including the Cincinnati CF center, carried out independent studies at the same time and provided data. Among the problems cited in the report of the Collaborative Study were the presence of blood in specimens, failure to store specimens properly prior to testing or retesting, and a high incidence of false-positive test results among premature infants. They concluded the paper strip test, while useful in detecting albumin in meconium, was not sufficiently accurate alone to determine the indication for sweat chloride testing and recommended against its use in mass screening procedures until further data were obtained.

We believe meconium testing in our hands avoided some of the problems encountered in the Collaborative Study. All testing was carried out in a central laboratory. No attempt was made to judge the degree of positiveness of the paper strip test, but all samples that were not clearly negative were further tested for albumin content by quantitative immunodiffusion. The introduction of a quantitative test for albumin between paper strip testing and sweat chloride testing brought the ratio of confirmed patients with CF to albumin positive patients to slightly over 1:5. All paper strip test-positive specimens were also tested for the presence of blood. Relatively few were grossly contaminated because specimens were not collected in the delivery room. Our data are similar to those of the Collaborative Study in that low-birth-weight infants accounted for approximately half the meconium specimens with albumin content greater than 12 mg/g.

Follow-up of low-birth-weight infants presented some problems. Private physicians were routinely notified of infants having albumin over 12 mg/g and sweat chloride tests, free of charge, were recommended. Ninety-five percent of full-term infants had follow-up sweat chloride tests. Among low-birth-weight infants, only 45% had sweat chloride tests; 23% died prior to testing, and 32% were not referred for testing. This response

may reflect the fact that community physicians were less concerned about the likelihood of CF in their patients with low birth weights. Gelatin liquefaction as a test for proteolytic activity may be useful in reducing the number of infants called back for sweat chloride determinations.

Our preliminary testing of CF meconium specimens with positive paper strip tests confirmed the report by Antonowicz et al.[13] Our screening procedure differed from theirs only in that we used a longer incubation period at room temperature because of the large number of tests performed each day. Every specimen that showed any lactase activity was retested. There was a high proportion of positive lactase tests, relatively few of which showed increased levels of albumin. Those with low levels of albumin were readily eliminated by quantitative albumin measurements, and the incidence of infants who required sweat chloride determinations was similar to that found using the paper strip test for primary screening. There is considerable discrepancy between the reported incidence of CF, about 1:2000 in whites, and the final diagnosed incidence of 1:4,600 in white, full-term infants found after further study of lactase test-positive specimens. Prior to beginning the screening program, about 50% of the patients in the Cincinnati CF clinic were diagnosed by 18 months of age. No infants are known to have been missed during the period of lactase screening, other than the two described. Both came to our attention during the first 2 to 3 months of life. We are, however, concerned over the low yield of positive results using the lactase test as a primary screening method, and have stored the meconium specimens frozen in order that they may be retested if affected patients are found later. Seventy-five percent to 85% of the infants found to have CF during the period of March 1975 to October 1979 were identified by meconium screening. We do not know if the lower incidence of positively identified infants with CF during the past two years is a chance finding, or if affected infants were missed. It may be that no procedure based on meconium will prove ideal. Infants who have normal proteolytic activity, and presumably normal pancreatic function, will show negative reactions to any test based on increased levels of protein. The chief advantage of the lactase test is that the commercial test strip for detection of glucose is much cheaper than the commercial test strip for albumin. The chief disadvantage is the large number of positive test results, which must be studied further.

Until the basic genetic lesion is identified, it will be difficult to formulate a more specific test. Until a definitive test is available, it seems inadvisable to recommend mass newborn CF screening along the lines of current practice for phenylketonuria and other inborn errors of metabolism. On the other hand, if Warwick[10] is correct in his claim that there is a high mortality among undiagnosed patients with CF during the first two years of life, early diagnosis of even 75% of the affected infants seems sufficient to justify the effort.

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BMC Test Meconium Strips used for the preliminary phase of testing were provided by Bio-Dynamics Division of Boehringer Mannheim Co, Indianapolis.

Personnel in the newborn nurseries of Bethesda Hospital, Christ Hospital, Cincinnati General Hospital, Good Samaritan Hospital, Jewish Hospital, and Mercy Hospital, Cincinnati, gave invaluable assistance in collecting and storing specimens. Local pediatricians referred patients for sweat chloride measurements. Anne Schaumberg, Jamie Campbell, Margaret Miller, and David Ringel carried out the screening tests.

References

1. Green MN, Shwachman H: Presumptive tests for cystic fibrosis based on serum protein in meconium. *Pediatrics* 41:989-992, 1968.

2. Davidson AG, Anderson CM: Diagnosis of cystic fibrosis. *Br Med J* 4:362-364, 1971.

3. Hellsing K, Kollberg H: Analysis of albumin in meconium for early detection of cystic fibrosis: A methological study. *Scand J Clin Lab Invest* 33:333-340, 1974.

4. Stephan U, Busch EW, Dannemann R: Ein neuer 'screening test' auf mukoviszedose Nachweis des erhohten Albumingehaltes im Mekonium. *Pediatr Prax* 12:487-490, 1973.

5. Stephan U, Busch EW, Kollberg H, et al: Cystic fibrosis detection by means of a test strip. *Pediatrics* 55:35-38, 1975.

6. Holsclaw DS, Berry HK, Bruns WT, et al: Meconium screening for cystic fibrosis: A collaborative study, in *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1977, p 54.

7. Antonowicz I, Ishida S, Shwachman H: Studies in meconium: Disaccharidase activities in meconium from cystic fibrosis patients and controls. *Pediatrics* 56:782-787, 1975.

8. Westler WB, Neal JL: Assay of proteolytic activity by gelatin liquefaction (trypsin assay by gelatin liquefaction). *Clin Chim Acta* 78:151-157, 1977.

9. Shwachman H, Antonowicz I, Mahmoodian A: Studies in meconium: An approach to screening tests to detect cystic fibrosis. *Am J Dis Child* 132:1112-1114, 1978.

10. Warwick WJ: Ascertainment of CF in Minnesota, in *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1979, p 88.

11. Lubin AH, Bonner JL: Growth parameters compared with time of diagnosis in CF, in *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1978, p 71.

12. Palmer J, Huang N, Laraya-Cussay LR, et al: Long-term follow-up of patients with CF diagnosed at birth. *Cystic Fibrosis Club Abstracts*. Rockville, Md, Cystic Fibrosis Foundation, 1978, p 83.

13. Antonowicz I, Ishida S, Shwachman H: Screening for cystic fibrosis. *Lancet* 1:746-747, 1976.

Surgical Treatment of Gastroesophageal Reflux in Children

Results of Nissen's Fundoplication in 100 Children

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• One hundred children underwent Nissen's fundoplication for complications of gastroesophageal reflux. Indications for fundoplication included refractory pneumonia, apneic spells, intractable vomiting, failure to thrive, esophagitis, esophageal stricture, and Sandifer's syndrome. Except for those with life-threatening complications, fundoplication was performed only in those who had failure with a strict medical antireflux regimen. Four patients were not helped by operation or had a recurrence of symptoms. Of these, three with refractory pneumonia were judged to be failures of selection since reflux was absent postoperatively. The fourth had massive reflux and recurrent vomiting. Eight other patients had radiologic evidence of reflux postoperatively. Six of these were asymptomatic and two had minor symptoms. There was one death and 11 postoperative complications.

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In the past few years, the diagnosis of gastroesophageal reflux (GER) has been made in children with increasing frequency. This increased recognition has resulted from the growing awareness that reflux is the cause of a varied group of significant disorders in children. It has also stemmed from more reliable detection of GER radiologically as improved techniques have been developed and disseminated.

A number of complications may result from GER. Vomiting, failure to thrive, recurrent pneumonia, and esophageal stricture have long been recognized. More recently, reflux has been incriminated as a cause of recurrent bronchitis, asthma, respiratory arrest, the sudden infant death syndrome,[1] Sandifer's syndrome, and protein-losing enteropathy.[2] Reflux may cause movement disorders that may be confused with seizures.[3] Symptomatic reflux esophagitis seems to be more common in childhood than previously suspected.

The majority of patients with GER do not have serious complications. Most infants suffer only from regurgitation, which responds readily to postural and dietary treatment. Some children with reflux are asymptomatic. Surgical treatment should be reserved for those patients with complications of GER that fail to respond to medical treatment or who have life-threatening complications.

Coincident with the increased frequency of diagnosis of reflux, Nissen's fundoplication has emerged as the operation of choice for patients in whom an antireflux procedure is necessary. This operation has consistently proved to have the highest rate of success and the fewest number of recurrences.[4]

At the Boston Floating Hospital, the number of patients seen annually with the diagnosis of GER has increased dramatically in the past five years, largely because of improvements in radiologic technique that have led to increased clinical awareness on the part of the referring physicians. Whereas a few years ago only a handful of patients were seen in whom the diagnosis was made, now more than 400 new cases of GER are seen annually. Few of these patients come to operation. Ninety percent are successfully treated medically.

In the five-year period ending in March 1979, a total of 100 children, aged 1 month to 13 years, underwent Nissen's fundoplication[5] at the Boston Floating Hospital for complications of GER. Ninety-six patients have been observed for a year or more. No failures or complications have appeared after six months in this group.

PATIENTS AND METHODS

Diagnosis

The diagnosis of GER was made by barium swallow roentgenogram in every patient. In experienced hands, GER is readily demonstrated radiologically. A diagnosis of GER was not made unless multiple episodes of reflux were seen under standardized conditions, as described by McCauley et al.[6] The patient is examined in the supine position without pressure on the abdomen or placing the head in a down position. An adequate amount of barium (equal to a normal feeding) must be given, and the patient must be relaxed. Reflux was not considered significant unless the patient's symptoms and other findings were consistent with this diagnosis.

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In 17 patients with recurrent pneumonia and in 21 patients with apneic spells, 24-hour pH probe study was carried out. The probe was placed in the upper third of the esophagus to detect reflux to the upper part of the esophagus that could potentially reach the larynx and be aspirated. The frequency of episodes of reflux and its relationship to the patient's position and thickening of feedings were determined.

Manometric evaluation of esophageal function was not performed in these patients. Previous studies have shown that lower esophageal sphincter pressure is not more reliable as an indicator of significant reflux,[7] while it is more cumbersome and uncomfortable for the patient.

If esophagitis was suspected, the diagnosis was established by biopsy at esophagoscopy. All patients undergoing operation for esophagitis had esophagitis by visual examination through the esophagoscope, confirmed by histologic examination in each case.

Selection for Operation

Patients with symptomatic reflux were initially treated with a strict regimen of medical therapy. Often, prior treatment had been casual or minimal: "Prop him up for one-half hour after feedings," or "Put a little cereal in the formula." In persistently symptomatic cases, rigid adherence to the principles outlined by Carre 20 years ago are necessary.[8] All of these are important. First, there should be 24-hour positioning in the upright posture. This may be obtained by placing the infant in a seat at 60° or strapping him prone on a board at 45°. Second, all liquid feedings must be thickened. Effective thickening requires the addition of 15 mL of cereal to each 30 mL of formula. Third, the volume of feedings is decreased to prevent overdistention of the stomach. The frequency of feedings may need to be increased (eg, 90 mL every three hours instead of 120 mL every four hours). Patients whose sole symptom is vomiting will respond to this regimen 80% to 90% of the time. Except for patients with strictures and those with life-threatening apneic spells, surgical treatment was reserved for failures of medical therapy—patients who had persistent serious symptoms despite treatment.

Specific Indications for Surgical Treatment

Refractory Pneumonia (40 Patients).—In addition to demonstrated reflux, these patients had characteristic patterns of aspiration. The pneumonia was typically migratory, involving different segments of the lung at different times. Usually it was diffuse, but it was localized to a single lobe on occasion. Typically, the bacterial flora was not specific and the response to antibiotic therapy was sluggish or nonexistent. Two patterns of pneumonia have been observed—refractory and recurrent.

Patients with refractory reflux pneumonia were usually young infants who experienced a fairly severe pneumonia, often bilateral, which did not clear with medical treatment. In some cases, this was quite severe, necessitating intensive care and ventilatory assistance. Most of the young infants coming to operation in this series were in this category. These patients were failures of medical therapy of reflux. A few responded to continuous aspiration of the stomach with a nasogastric tube and parenteral nutrition, but promptly suffered a relapse when thickened feedings were begun.

The second pattern of recurrent pneumonia was more typical in the older child. These patients had frequent hospitalizations because of pneumonia, often three or four times in one year. Different lobes would be involved, and bacteriologic flora varied. Often, normal mouth organisms were found. Usually these patients also had increased tracheobronchial secretions—"rattles" and "congestion"—between episodes of pneumonia, frequent upper respiratory tract infections, otitis media, and chronic cough. Several had recurrent bronchitis, and two had recurrent severe attacks of asthma.

Since the vast majority of patients with GER do not experience pneumonia, it is assumed that these individuals had an additional abnormality, such as abnormal laryngeal protective reflexes that fail to prevent aspiration, particularly at night. An antireflux operation does not alter this second abnormality, but it does eliminate the possibility of gastric contents being delivered to the larynx.

Apneic Spells (16 Patients).—Respiratory arrest may be caused by GER.[1] Again, there are two patterns—minor and life-threatening. Minor apneic spells are characterized by frequent choking with apnea and cyanosis that responds to stimulation. The child is described by the mother as having difficulty getting his breath, not merely that he stops breathing from time to time. Patients have been selected for surgical treatment if such spells increased in frequency despite adequate medical treatment. These represented about one half of the patients who were operated on because of apnea.

Life-threatening apneic spells were seen in the other half. These patients suffered a major respiratory arrest that required resuscitation and hospitalization. In a typical spell, the child was noted to appear startled and silently struggling to breathe. He became agitated, reddened, and sometimes thrashed about; he then became pale, cyanotic, and limp. It is apparent to the observer that the patient is trying to breath and unable to do so. Many of these patients had one or more additional spells in the hospital where they were observed by medical personnel. Medical treatment was not tried in these patients because of an unacceptably high failure rate (there is at least one reported death from failure of positional and dietary therapy in a child with GER and a previous apneic spell).[9] In addition, parents and pediatricians found it unacceptable.

Most patients with apneic spells had no vomiting, and thus reflux was often not suspected as the cause. Further, most of them did not have pneumonia, so that hypoxia seems unlikely as the mechanism for apnea. As with pneumonia, we postulate that there is a second abnormality, again most likely immature laryngeal reflexes, but the evidence for this is only circumstantial. The evidence linking GER to the sudden infant death syndrome has been previously presented.[1,9] All of the patients in the current series were under 1 year of age, and those with life-threatening spells were all under 6 months of age.

Intractable Vomiting (13 Patients).—In general, these were older children. Half of them were mentally retarded, and vomit-

Results of Nissen's Fundoplication in 96 Patients

Indication	No.	Failed	Minor Symptoms	Radiologic Recurrence
Refractory pneumonia	40	3*	0	2
Apneic spells	16	0	0	1
Intractable vomiting	13	1	0	3
Failure to thrive	6	0	0	0
Esophagitis	10	0	1	1
Stricture	6	0	0	1
Sandifer's syndrome	5	0	1	1
Total	**96**	**4**	**2**	**9**

*None of these patients had radiologic recurrence.

ing was a major problem in their management. The others were children with multiple episodes of vomiting daily in whom medical treatment was unsuccessful. They had failed to "grow out of" reflux by 12 to 18 months. Several were older children with a lifelong history of vomiting in whom the diagnosis of reflux had not been made earlier.

Failure to Thrive (Six Patients).—These patients ranged in age from 3 months to 2 years. All failed to respond to medical therapy and exhibited progressive growth failure. All were below the fifth percentile in weight at the time of operation. All had a minimum of two months of medical therapy with lack of response before the decision to perform fundoplication was made. In several young patients, an additional trial of several weeks of in-hospital treatment with careful calorie counts was performed prior to surgery.

Esophagitis (Ten Patients).—These patients' symptoms manifested in several ways. Five had epigastric and substernal pain, three had dysphagia, two had bleeding, and one had perforation of an esophageal ulcer. They ranged in age from 4 months to 13 years. All (except the patient with the perforated ulcer) underwent a trial of medical therapy, including antacids, prior to selection for operation. All had the diagnosis confirmed by biopsy.

Stricture (Six Patients).—These were all older children, the youngest being 4 years of age. Two thirds of them were mentally retarded. None complained of pain. All of these first came to medical attention because of dysphagia. In one patient, psychotherapy had been recommended on the assumption that his dysphagia was emotional in origin. In addition to the stricture, reflux was demonstrated by barium study in each patient. Esophagitis at the level of the stricture was confirmed by biopsy.

Sandifer's Syndrome (Five Patients).—Spasmodic torticollis associated with hiatal hernia was described by Sutcliffe in 1969.[10] It is now recognized that GER, not hiatal hernia, is the causative factor. In our experience, it is not rare. All of our patients have had mild esophagitis proved by biopsy, and all those coming to operation were failures of medical therapy, including the use of antacids. Progressive facial deformity was the indication for surgical treatment.

RESULTS

Ninety-six patients have been observed since operation. Ninety-two (96%) have had a successful result. All patients have been followed up for at least one year. A follow-up upper gastrointestinal tract roentgenographic series was performed six weeks or more after fundoplication to detect possible recurrence of reflux.

Success or failure of fundoplication may be evaluated by a number of criteria: symptomatic, radiologic, manometric, pH, and histologic. Clearly, the important question is whether the patient has been relieved of his symptoms. This may not require complete elimination of reflux as determined radiologically. Consequently, the operation has been considered successful if the patient had no symptoms, even if there was a small amount of radiologic reflux postoperatively (six patients).

Failure to relieve symptoms by fundoplication may be the result of two possible causes: failure of the fundoplication to stop reflux, or failure of proper selection of the patient for the operation. That is, the operation has eliminated the reflux, but the symptoms persist. In these patients, GER was probably not the causative mechanism, or pathologic changes had progressed beyond reversibility and the operation was performed too late to be of value.

Patients with stricture represent a special group. Although elimination of reflux almost always leads to significant improvement, and is essential for successful treatment of the stricture, it is rarely sufficient by itself. All of our stricture patients needed esophageal dilations. The follow-up results are summarized in the Table.

Refractory Pneumonia

Thirty (75%) of the 40 patients have had no further episodes of pneumonia. In these patients, fundoplication resulted in an abrupt change in their patterns of persistent or recurrent pulmonary disease. Two had mild GER by follow-up barium study. Seven patients (18%) have had one subsequent episode of pneumonia, but are considered to have had successful results since the pattern of recurrent infections was broken and they subsequently have been well with relief of recurrent "congestion" and other symptoms. None of these patients had recurrent GER by roentgenographic examination.

In three patients (8%), fundoplication had no effect on their pulmonary disease. One patient, operated on at age 2 months because of severe nonresolving pneumonia, was operated on too late. He showed no improvement after fundoplication and eventually died of pulmonary insufficiency. The second was subsequently found to have a T-cell immunodeficiency and suffered recurrent pulmonary and cutaneous infections until he died three years later. In the third patient, there was no apparent reason for his recurrent episodes of pneumonia, but reflux was clearly not the primary mechanism. None of these three patients had radiologic evidence of recurrent reflux. Thus, they represent failures of selection.

Apneic Spells

None of the 16 patients operated on for apneic spells has had another spell. A minor degree of reflux was noted by follow-up barium study in one of these asymptomatic patients.

Intractable Vomiting

One of the 13 patients, the youngest in this group, experienced recurrence of vomiting approximately two months after fundoplication. Radiologic examination showed breakdown of the surgical repair with recurrent massive reflux. He was treated successfully with positional and dietary measures and has subsequently been free of symptoms without treatment for more than two years. He is considered a failure of fundoplication. The remaining 12 patients have had no further vomiting. Two asymptomatic patients demonstrated recurrent GER by barium roentgenogram two and three years after operation.

Failure to Thrive

There were no failures in this group of six patients. Reversal of the downward weight trend occurred following fundoplication in each patient, usually within two weeks after operation.

Esophagitis

One of ten patients has had minor symptoms with occasional fussiness,

which may be related to persistent reflux demonstrated by roentgenogram. His condition is considered to be improved, but not cured. The other nine patients are free of symptoms.

Stricture

All six patients have shown improvement, but all have required multiple dilations. One patient required segmental resection of the stricture after repeated dilations during a one-year period. He has subsequently been symptom-free for more than two years.

Sandifer's Syndrome

Facial deformity was corrected in all five patients. One patient has grade 1 persistent radiologic reflux with occasional head tilting.

Complications

There was one death. A 7-month-old boy was operated on for failure to thrive. Postoperatively, he experienced fulminant *Haemophilus influenza* pneumonia and died on the fourth postoperative day.

There have been seven operative complications (7%). Two of these were nonspecific for fundoplication—one wound dehiscence and one patient in whom a leak from a gastrostomy developed. Five were specifically related to the type of operative procedure. A leak at the suture line developed in two patients, requiring reoperation. One patient had a fundoplication that was too tight. This responded to a single dilation. Two patients had postoperative gastric stasis requiring prolonged intubation. Each responded to a short course of metoclopramide therapy.

Four patients had late complications (4%). Three of these were nonspecific—intestinal obstruction secondary to adhesions a month or more after operation. All required reoperation. The fourth patient experienced herniation of the fundoplication into the chest and required reoperation.

Several patients had less serious side effects or complications that required treatment. Five patients suffered from "gas bloat"—fullness and fussiness after feeding. These responded to treatment with simethicone with spontaneous disappearance of the symptom in four to six weeks. All of these were infants. Four other infants experienced diarrhea significant enough to delay discharge from the hospital. In two patients it was prolonged, but gradually subsided. The mechanism of diarrhea is unclear. There was no evidence of delayed gastric emptying to suggest vagal injury. It may be that inability to belch swallowed air led to intestinal hyperperistalsis. Evaluation of diarrhea is further compounded by the fact that the incidence in this series of patients was no greater than that seen in children of the same age hospitalized for other reasons and not operated on.

CONCLUSIONS

Nissen's fundoplication is a safe and effective antireflux procedure that can be expected to eliminate GER in all but a small percentage of those in whom it is used. Properly selected, patients with all of the recognized complications of reflux unresponsive to medical therapy will be relieved of their symptoms. Nevertheless, as with any major surgical operation, the potential for complications is such that the operation should be reserved for those who have life-threatening complications or those who are unresponsive to medical therapy.

Nonproprietary Name and Trademarks of Drug

Simethicone—*Antifoam A Compound, Mylicon, Silain.*

References

1. Leape LL, Holder TM, Franklin JD, et al: Respiratory arrest in infants secondary to gastroesophageal reflux. *Pediatrics* 60:924-928, 1977.
2. Herbst JJ, Johnson DG, Oliveros MA: Gastroesophageal reflux with protein-losing enteropathy and finger clubbing. *Am J Dis Child* 130:1256-1258, 1976.
3. Bray PF, Herbst JJ, Johnson DG, et al: Childhood gastroesophageal reflux: Neurologic and psychiatric syndromes mimicked. *JAMA* 237:1342-1345, 1977.
4. Demeester TR, Johnson LF, Kent AH: Evaluation of current operations for the prevention of gastroesophageal reflux. *Ann Surg* 180:511-525, 1974.
5. Nissen R: Gastropexy and 'fundoplication' in surgical treatment of hiatus hernia. *Am J Dig Dis* 6:954, 1961.
6. McCauley RGK, Darling DB, Leonidas JC, et al: Gastroesophageal reflux in infants and children: A useful classification and reliable physiologic technique for its demonstration. *AJR* 130:47-50, 1978.
7. Boix-Ochoa J, in Gellis SS (ed): *Gastroesophageal Reflux: Report of the 76th Ross Conference on Pediatric Research.* Columbus, Ohio, Ross Laboratories, 1979, pp 65-69, 73-76.
8. Carre IJ: Postural treatment of children with a partial thoracic stomach ('hiatus hernia'). *Arch Dis Child* 35:569-580, 1960.
9. Herbst JJ, Book LS, Bray PF: Gastroesophageal reflux in the 'near miss' sudden infant death syndrome. *J Pediatr* 92:73-75, 1978.
10. Sutcliffe J: Torsion spasms and abnormal postures in children with hiatus hernia: Sandifer's syndrome. *Progr Pediatr Radiol* 2:190-197, 1969.

Congenital Leukemoid Reaction Followed by Fatal Leukemia

A Case With Down's Syndrome

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• A serial clinical, hematologic, and cytogenetic study was done on a baby with Down's syndrome in whom a myeloid leukemoid reaction developed at birth that spontaneously regressed within a month only to relapse two years later to an acute undifferentiated stem cell leukemia. He died 1½ months after onset. The unresolved controversy of the diagnosis of the congenital leukemia-like state is discussed. The importance of following up such patients with apparent remission of their congenital leukemia-like disorder is emphasized.

(*Am J Dis Child* 134:939-941, 1980)

The estimated incidence of congenital leukemia in Down's syndrome is three to 61 times that of the general population.[1,2] The high rate of spontaneous remission seen in such cases has led to the still unresolved controversy of whether the phenomenon is a true leukemia or a transient leukemoid reaction, the result of ineffective regulation of granulopoiesis.[3,4] The remission is permanent in most instances but rarely it is terminated by leukemic relapse five to 30 months later.[5,6] This case report illustrates this unusual course and highlights the controversy over the diagnosis of congenital leukemia in Down's syndrome.

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REPORT OF A CASE

This boy was born on April 13, 1977, at the University Hospital, Kuala Lumpur, Malaysia, after an uncomplicated term pregnancy. The mother was 41 years old and the father 46 years old. He had one sister, aged 7 years, who is well.

The birth weight was 2,968 g and there were obvious stigmata of Down's syndrome at birth. The baby was well but routine examination showed an enlarged liver, palpable 3 cm below the right costal margin. The spleen and the lymph nodes were not palpable and there was no pallor, petechiae, or skin nodules. Results of fundi examination were normal.

Laboratory investigations done on the first few days of life included the following values: hemoglobin, 15.3/dL; platelet, 44,000/cu mm; total WBCs, 24,200/cu mm; myeloblasts, 13%; neutrophils, 76%; lymphocytes, 8%; monocytes, 3%; and reticulocytes, 5%. Both mother and the baby were blood group A, Rh-positive. Direct Coomb's test was negative, glucose-6-phosphate dehydrogenase level (G6PD) was normal, and urine tests were negative for urobilinogen and bilirubin. Karyotyping showed 47 XY, trisomy 21. The bone marrow examination at day 4 showed a very cellular marrow with a shift of granulopoiesis to the left. There were about 15% myeloblasts that were negative for PAS and peroxidase. The leukocyte alkaline phosphatase score was 216. Megakaryocytes were scarce. In view of the good clinical state, the lack of pallor and the small percentage of blastforms in the bone marrow, a diagnosis of myeloid leukemoid reaction was made. Serology titers for congenital toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis were not significant and blood culture was negative.

During a period of one month, the liver size and the platelet count spontaneously returned to normal, and the blastforms disappeared from the peripheral blood. Results of repeated bone marrow examination were normal.

The child was followed up regularly and remained relatively well with good physical growth but mild developmental retardation. At the age of 2 years, he was noted to be very pale with generalized purpura. The liver was enlarged 4 cm and the spleen was enlarged 4 cm below the costal margin. Laboratory values were as follows: hemoglobin, 5.2 g/dL; platelets, 11,000/cu mm; WBCs, 23,000/cu mm; blastforms, 10%; neutrophils, 16%; lymphocytes, 74%; and reticulocytes, 0.1%. The bone marrow was

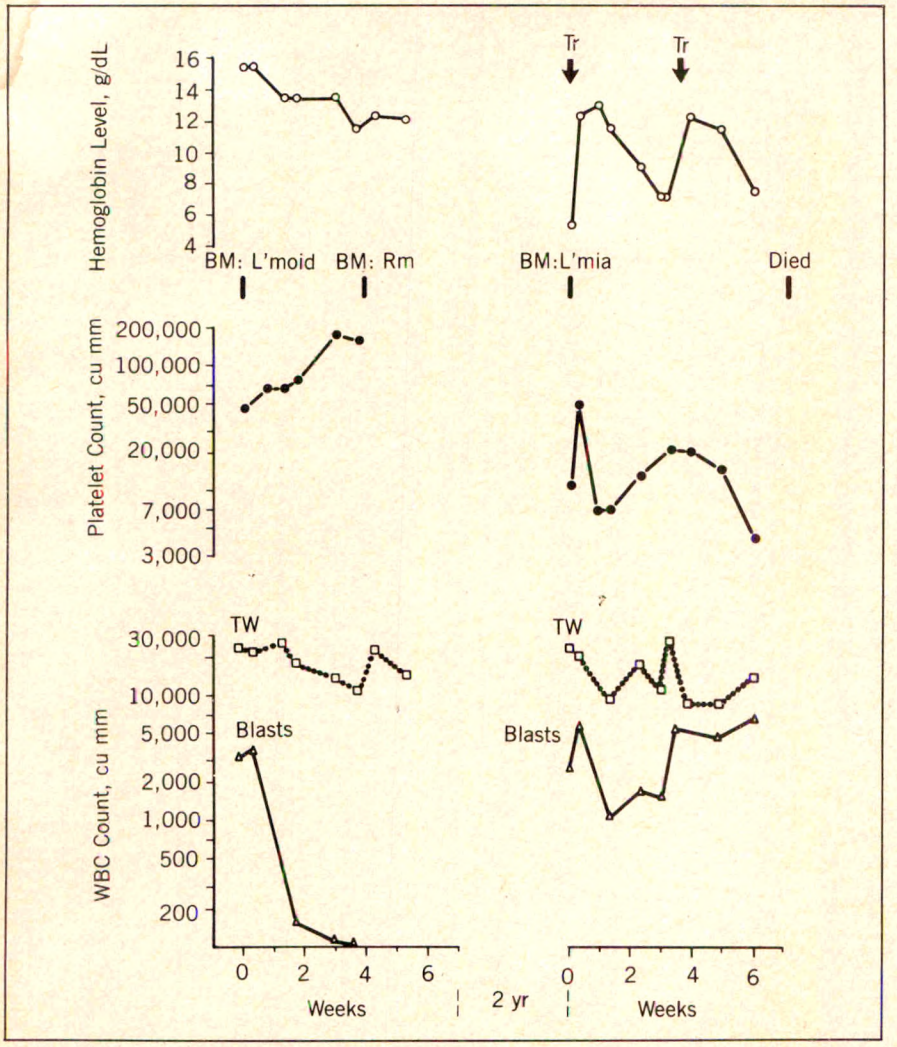


Fig 1.—Serial blood cell counts on child with Down's syndrome: BM indicates bone marrow; Tr, packed-cell transfusion; L'moid, myeloid leukemoid reaction; Rm, remission; L'mia, acute undifferentiated leukemia; and TW: total WBC count.

hypercellular with predominantly myeloid elements but reduced erythropoiesis and thrombopoiesis. The differential cell count of the WBCs was as follows: 56% blastforms that were occasionally positive for PAS and peroxidase; 28% promyelocytes, myelocytes, and metamyelocytes; and 16% lymphocytes. There were a few erythroblasts. The diagnosis was that of an undifferentiated stem cell leukemia. Repeated chromosome culture showed 47 karyotype with trisomy 21 in the majority of the cells but in addition, occasional cell lines showed 48 or 49 chromosomes. However, the nature of the additional chromosomes was uncertain.

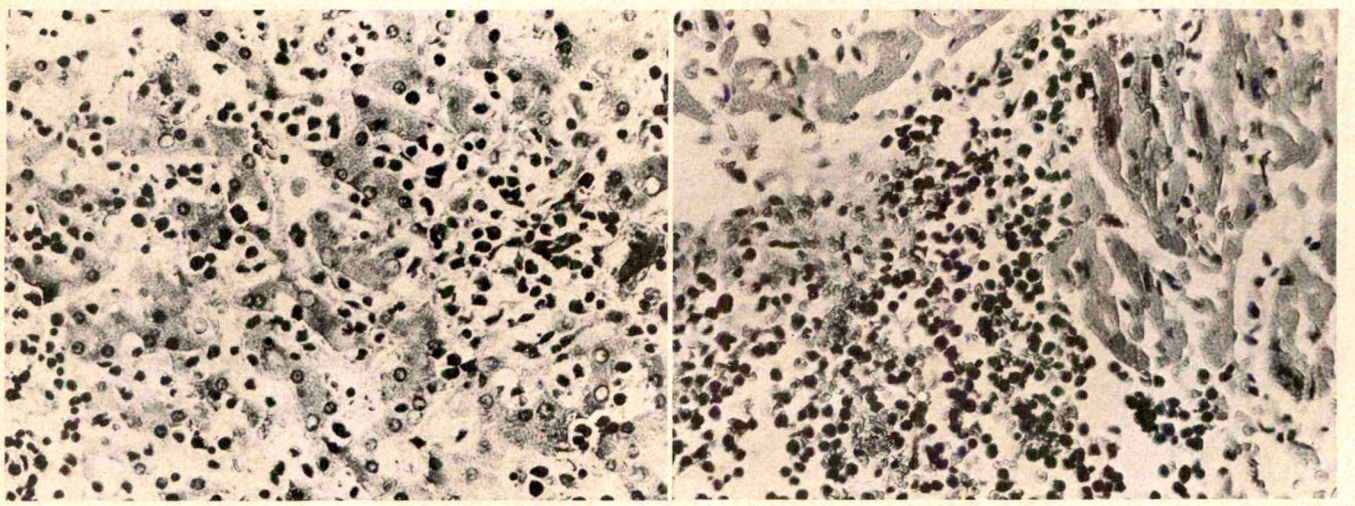
Treatment was withheld with the parents' consent. The patient's condition had a progressively downhill course leading to his death 1½ months after the leukemia was diagnosed (Fig 1).

Autopsy showed terminal bronchopneumonia and widespread mononuclear cell infiltration of the liver, heart, kidney, and lymph nodes in the mediastinum and abdomen (Fig 2). The brain and the gut were normal.

COMMENT

The controversy regarding the nature of the abnormal myelopoiesis found in newborn infants with Down's syndrome remains unresolved. It may represent a transient myeloid leukemoid reaction, the result of ineffective regulation of granulopoiesis masquerading as congenital leukemia.[3,7,8] This view is mainly based on the high spontaneous remission rate observed in such patients, the majority of whom achieved permanent re-

Fig 2.—Photomicrograph of sections of liver (left) and heart (right) at autopsy showing infiltration by mononuclear cells (hematoxylin-eosin, original magnification ×400).



ission within one to five months from birth. Many who died years later of unrelated disorders were found on autopsy to be free of leukemia.[3,4,9] Such behavior is atypical of true leukemia. The existence of congenital leukemia was questioned on the basis that it may be a reaction to such stimuli as sepsis or blood group incompatibilities that were found in some earlier reports.[7,10] In addition to the occurrence of leukemoid reaction, there were reports of other less common myeloproliferative disorders occurring among newborns with Down's syndrome, such as polycythemia and thrombocytosis.[11,12] To further support this hypothesis were the observations that there were ultrastructural, enzymatic, and functional differences between the myeloblasts of patients with Down's syndrome as opposed to those without this syndrome.[13,14]

It is also possible that the abnormal granulopoiesis represents true leukemia in that the usual clinical and laboratory criteria for leukemia are satisfied—pallor, hepatosplenomegaly, purpura, skin nodules, and blastforms in the peripheral blood and bone marrow. It was suggested that the high rate of spontaneous remission was not incompatible with the diagnosis but should instead stimulate research as to why patients with Down's syndrome should recover from leukemia.[4] Moreover, there were some patients who died of congenital leukemia without achieving a remission.[6] Although permanent remission is the rule, there are occasional reports of patients with Down's syndrome who went into spontaneous remission initially only to die five to 30 months later of frank leukemia.[5,6] This unusual clinical course was followed in our patient. The transient congenital blood disorder was probably due to a myeloid leukemoid reaction as the baby was well, the liver was only slightly enlarged, and there were only about 15% blastforms in the bone marrow, although the thrombocytopenia was moderately severe. However, obvious stimuli to this "reaction" could not be identified as there was no blood group incompatibility, G6PD deficiency, hemolysis, intrauterine, or neonatal sepsis. The fact that a true leukemia developed after two years illustrates the importance of close follow-up of such cases for as long as possible.

The importance of the 48 or 49 chromosomes in occasional cell lines seen on chromosomal cultures of peripheral blood during the leukemic phase in this patient is unknown. In a similar patient with Down's syndrome with trisomy 21, where serial cytogenetic studies were done, it was found that with exacerbation of the leukemia the cell line with 48 chromosomes (the additional chromosome being in the six to 12 group) became the major line in the bone marrow.[5] Unfortunately, in our patient, the identity of the additional chromosomes could not be ascertained.

Khuan-Leng Lam, FRCP(O) helped in the criticism of this article.

References

1. Krivit W, Good RA: Simultaneous occurrence of mongolism and leukemia. *Am J Dis Child* 94:289-293, 1957.

2. Wald N, Borges WL, Li CC, et al: Leukaemia associated with mongolism. *Lancet* 1:1228, 1961.

3. Ross JD, Maloney WC, Desforges JF: Ineffective regulation of granulopoiesis masquerading as congenital leukemia in a mongoloid child. *J Pediatr* 63:1-10, 1963.

4. Engel RR, Hammond D, Eitzman DV, et al: Transient congenital leukemia in seven infants with mongolism. *J Pediatr* 65:303-305, 1964.

5. Honda F, Punett HH, Charney E, et al: Serial cytogenetic and hematologic studies on a mongol with trisomy 21 with acute congenital leukemia. *J Pediatr* 65:880-887, 1964.

6. Conen PE, Erkman B: Combined mongolism and leukemia: Report of eight cases with chromosome studies. *Am J Dis Child* 112:429-443, 1966.

7. Kauffman HJ, Hess R: Does congenital leukaemia exist? *Br Med J* 1:867-868, 1966.

8. Rosner F, Lee SL, written for the Acute Leukemia Group B: Down's syndrome and acute leukemia: Myeloblastic or lmyphoblastic? Report of 43 cases and review of the literature. *Am J Med* 53:203-218, 1972.

9. Schunk GJ, Lehman LW: Mongolism and congenital leukemia. *JAMA* 155:250-251, 1954.

10. O'Connor RE, McKay RN, Smith J: Congenital leukemia with septicemia as a terminal event. *Am J Dis Child* 88:740-742, 1954.

11. Weinberger MM, Oleinick A: Congenital marrow dysfunction in Down's syndrome. *J Pediatr* 77:273-279, 1970.

12. Miller JM, Sherrill JG, Hathaway WE: Thrombocythemia in the myeloproliferative disorder of Down's syndrome. *Pediatrics* 40:847-850, 1967.

13. Nagao T, Lampkin BC, Hug G: A neonate with Down's syndrome and transient abnormal myelopoiesis: Serial blood and bone marrow studies. *Blood* 36:443-447, 1970.

14. Rosner F, Ong BH, Paine RS, et al: Biochemical differentiation of trisomic Down's syndrome (mongolism) from that due to translocation. *N Engl J Med* 273:1356-1361, 1965.

Immunologic Maturation in an Infant Born to a Mother With Agammaglobulinemia

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• **An infant born to a mother with agammaglobulinemia was followed up since birth to study immunologic maturation uninfluenced by circulating maternal antibodies. Immunoglobulin levels remained low and antibodies to immunizing antigens appeared late. These observations, together with findings in two other reported infants born to agammaglobulinemic mothers, suggest that transplacental maternal antibodies play little or no role in modulating newborn IgG production and that the delay in achieving normal levels of IgG are probably due to the immaturity of newborn B lymphocytes.**

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Most term neonates are born with adult levels of IgG acquired transplacentally from the mother. These provide temporary protection against many infectious agents until the infant can synthesize his own antibodies.[1,2] The exception is the infant born to a mother with agammaglobulinemia. We recently cared for such a child and because of his excellent clinical condition, a responsible mother, the possibility of suppressing endogenous IgG synthesis, and the favorable outcome in three similarly untreated infants,[3-5] we elected not to give the child γ-globulin injections. This also provided an opportunity to study an infant's immunologic maturation uninfluenced by maternal or exogenous γ-globulin.

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REPORT OF A CASE

The child's mother was a 22-year-old woman in whom upper respiratory tract infections developed during the third trimester of each of her two pregnancies (at ages 19 and 22 years, respectively). Her history showed no serious infections, early infantile deaths, arthritis, or consanguinity. During her second pregnancy, results of protein electrophoresis obtained during the third trimester revealed an absent γ-globulin spike; however, immunoglobulin levels were not measured. Although the delivery at a community hospital was uneventful, she continued to cough persistently. She was given γ-globulin injections, 5 mL every two weeks. Her immunoglobulin levels at the time of delivery were 98 mg/dL of IgG, 14 mg/dL of IgM, and 12 mg/dL of IgA. She was referred nine days postpartum to the UCLA Medical Center, Los Angeles, at which time her immunoglobulin levels were as follows: IgG, 164 mg/dL (normal, 1,158 ± 305 mg/dL); IgM, 25 mg/dL (normal, 99 ± 27 mg/dL); and IgA, 2 mg/dL (normal, 200 ± 61 mg/dL). Polio (viral neutralization) and tetanus titers were negative. T-cell enumeration (E rosettes) was 75% (normal range, 65% ± 10%) and B-cell enumeration (surface membrane Ig) was 3% (normal range, 15% ± 10%).

Results of studies to assess suppressor T cells and in vitro immunoglobulin synthesis indicated that her hypogammaglobulinemia was due to an intrinsic B-cell defect. Addition of normal T cells did not result in production of immunoglobulin by her B cells. Her T cells did not suppress normal B-cell in vitro immunoglobulin synthesis, nor were suppressor lymphokines produced. The methods are described elsewhere.[6]

The results of a physical examination were unremarkable, except for postnasal discharge and scarcity of lymph tissue. Sinus roentgenograms showed pansinusitis, and the chest films suggested a retrocardiac infiltrate. Her condition responded well to γ-globulin injections (0.7 mL/kg/mo) and administration of oral penicillin and nasal decongestants. Subsequently, she has been free of symptoms during ten months of follow-up, although her immunoglobulin levels have remained low. Repeated roentgenograms have been normal.

The propositus, a boy, was born on May 16, 1978, and weighed 2,640 g at birth. There were no postnatal difficulties. Measurement of immunoglobulin levels at birth revealed the following: IgG, 90 mg/dL; IgM, 24 mg/dL; and IgA, not detected. He was referred to UCLA at 9 days of age, along with his mother, for an immunologic evaluation. Results of these studies are given in the Table and the Figure. The immunoglobulin levels at that time were as follows: IgG, 100 mg/dL (normal, 1,031 ± 200 mg/dL); IgM, 6 mg/dL (normal, 11 ± 5 mg/dL); IgA, 2 mg/dL (normal, 2 ± 2 mg/dL); T cells, 62% (normal range, 65% ± 10%); and B cells, 16% (normal range, 15% ± 10%). In vitro lymphocyte stimulation with phytohemagglutinin was normal.

The child was robust and thrived. At 2

Immunization Schedule and Antibody Response

Age, mo	Vaccine: DPT*	Vaccine: Killed Polio	Antibody Titers: Polio I	Polio II	Polio III	Tetanus	Anti-B Isohemagglutinin
Birth	...	...	...	...	...	...	...
1	...	...	...	...	...	...	...
2	X	X	N	N	N	N	1:1
3	...	...	N	N	N	N	1:1
4	X	X	N	N	N	ND	1:1
5	...	...	N	1:16	1:16	ND	ND
6	X	X	N	N	N	1:32	ND
7	...	...	1:128	1:32	1:128	1:256	1:4
8	...	...	1:128	1:16	1:64	1:256	1:2

*DPT indicates diphtheria-pertussis-tetanus; N, negative titer (polio, < 1:4; tetanus, 0); ND, not done.

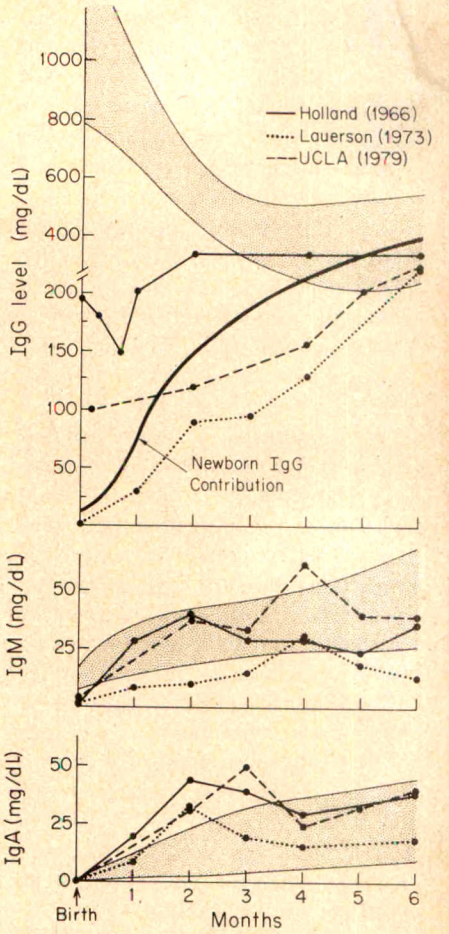
months of age he weighed 5.2 kg, and at 7 months of age he weighed 8.0 kg. Except for one mild bout of rhinitis at age 2 months, he was not ill. He was not given γ-globulin injections, but formula feedings were supplemented with donor breast milk until he was 5 months of age. Diphtheria-pertussis-tetanus and killed-polio vaccines were given at 2, 4, and 6 months of age (Table). Immunoglobulin levels, isohemagglutinin titers, and antibody response to poliovirus and tetanus antigen were followed serially. A Schick test was negative at 7 months of age, indicating the presence of antidiphtheria antibody.

An older female sibling, now 2 years old, also born in a small community hospital, had group B streptococcal sepsis at 3 days of age that required hospitalization and therapy for two weeks. Since it was not known at that time that the mother was hypogammaglobulinemic, no immunological studies were carried out. The child has subsequently done well. Immunoglobulin levels obtained on this child (age 2 years) at the time of the evaluation of the mother and propositus were as follows: IgG, 740 mg/dL (normal, 762 ± 209 mg/dL); IgM, 45 mg/dL (normal, 58 ± 23 mg/dL); and IgA, 40 mg/dL (normal 50 ± 23 mg/dL).

COMMENT

Immunoglobulin synthesis in the neonate is slow to develop. Contributing to this delay are the immaturity of the neonatal cells involved in immunoglobulin production, the possible inhibition from circulating maternal immunoglobulins, and the protected environment present in most newborns, which diminishes exogenous antigen contact.[7-10] Thus, endogenous IgG levels in infants of normal mothers are negligible at birth, climb to a level of 200 mg/dL at 2 months of age, and continue to rise, so that by age 1 year a value of 800 mg/dL is reached. It has been known for a long time that circulating maternal antibodies may interfere with selective antibody response in the infant. This interference is limited since newborns can respond to certain vaccines.[2,11,12] If a suppressive effect exists, then in the absence of circulating maternal antibodies one would expect infants from mothers with agammaglobulinemia to synthesize IgG earlier and thus achieve levels of endogenous IgG at comparable ages higher than those of children of normal mothers. In addition, the lack of maternal antibody interference should expose the child to increased antigenic stimulation, further providing impetus for increased antibody production. However, this expected increase in IgG level was not seen in our patient. Rather, his IgG level was slightly lower than the endogenous IgG levels seen in normal newborns during the first 8 months of life (Figure). His IgM and IgA levels were not significantly increased over normal values, either.

Similar observations have been made in two other children born to agammaglobulinemic mothers.[4,5] Indeed, the infant reported by Laursen and Christensen[5] had IgG levels below 100 mg/dL for the first 3 months of age, which by 5 months of age rose to a mere 150 mg/dL (Figure). In an early report, Bridges et al[3] noted that γ-globulin levels determined by electrophoresis were undetectable in a child from a mother with agammaglobulinemia until 42 days of life, and positive titers to *Salmonella* sp did not appear until 67 days of life, despite



IgG, IgM, and IgA levels in three infants born to agammaglobulinemic mothers (IgG values include small contribution from mother). Shaded areas represent Ig levels for normal infants (± 1 SD) and dark, solid line represents endogenous IgG from normal newborns.[1]

exogenous stimulation from bacterial colonization and repeated typhoid vaccinations. A second child born to this same mother did not produce detectable levels of γ-globulin until 28 days of life.[13] These observations and the response in our child suggest that transplacental maternal antibodies only play a minor role, if any, in modulating total IgG production in the neonate.

Bridges et al[3] attributed this lack of immunoglobulin and antibody formation to the absence of plasma cells. Indeed, plasma cells did not become abundant in these and normal infants until several months later. Recent studies to evaluate B- and T-cell interaction further elucidated the possible mechanisms for delayed IgG synthesis.[14,15] Hayward and Lawton[14] ob-

served that newborns have normal numbers of B cells of all classes, but that differentiation in vitro into plasma cells that synthesize IgG is impaired even when adult helper T cells are used. Moreover, newborn T cells suppress both adult and newborn B-cell differentiation and also do not help B-cell differentiation as effectively as do adult T cells. Thus, it seems that the limited IgG synthesis is both an intrinsic B-cell deficit and a T-cell regulatory phenomenon uninfluenced by exogenous IgG.

Could maternal T suppressor cells play a role in the less than expected IgG production in our child? Waldmann et al[16,17] suggested that some patients with common variable hypogammaglobulinemia have excess suppressor T cells, which are responsible for their diminished immunoglobulin production. Thus, if the mother had excess T-cell suppression causing her hypogammaglobulinemia, it is conceivable that these cells or a product of these cells could cross transplacentally and inhibit newborn B-cell differentiation. However, in vitro assessment of the mother did not demonstrate excess T-cell suppression or suppressor substances. Furthermore, this should be a short-lived effect. Therefore, it is unlikely that these factors were responsible for the slow IgG rise in our child. Whether maternal T-cell suppression played a role in the previously reported cases is not known, since these techniques were unavailable at that time.

Specific antibody response to polio and to tetanus vaccine were assessed in our child. A positive titer (polio $> 1:4$; tetanus $> 1:8$) was finally seen after three vaccinations. In normal infants, an antibody response develops in 80% after the first polio immunization (killed vaccine)[18] and in 85% to 92% a response develops after the second.[18,19] Immunization with tetanus toxoid is even more effective, ie, a 98% response rate after the first vaccination and nearly 100% conversion after the second vaccination.[20] The results given in the Table indicate that our infant's response was delayed. This is somewhat surprising, since he would be expected to respond at least as well as normal infants, and perhaps even better since maternal antibody interference was not a factor. Donor breast milk was given to supplement formula feedings to take advantage of possible anti-infective properties[21] contained therein. Although immunoglobulins contained in breast milk are not absorbed from the gut to an appreciable extent, thus not influencing the level of the infant's immunoglobulin, it is conceivable that the breast milk may have reduced colonization of coliform bacteria. This could have the effect of lessening antigenic stimulation and reducing immunoglobulin production.

It is interesting to note that the older sibling of our patient had neonatal group B streptococcal sepsis. The mother was presumably agammaglobulinemic at that time and was unable to make antibodies. Thus, the older child could have been vulnerable to this organism since Baker and associates[22-24] have suggested that maternal antigroup B streptococcal antibodies will protect the infant against this organism. Following this episode, the older child did not have further problems with infection.

In summary, despite low levels of IgG, our patient did well clinically and had only one mild respiratory infection in the first year. No special precautions were taken other than to supplement formula feedings with donor breast milk for five months. Other infants born to agammaglobulinemic mothers have not been unduly susceptible to infections.[3-5]

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Studies to assess suppressor T cells and in vitro immunoglobulin synthesis were performed by Andrew Saxon, MD, of the Department of Medicine, UCLA School of Medicine, Los Angeles.

References

1. Miller ME, Stiehm ER: Phagocytic, opsonic and immunoglobulin studies in newborns (medical progress). *Calif Med* 119:43-63, 1973.

2. Bellanti JA, Hurtado RC: Immunology and resistance to infection, in Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, WB Saunders Co, 1976, pp 33-70.

3. Bridges, RA, Condie RM, Zak SJ, et al: The morphological basis of antibody formation development during the neonatal period. *J Lab Clin Med* 53:331-357, 1959.

4. Holland NH, Holland P: Immunologic maturation in an infant of an agammaglobulinemic mother. *Lancet* 2:1152-1155, 1966.

5. Laursen HB, Christensen MF: Immunoglobulins in normal infant born of severe hypogammaglobulinemic mother. *Arch Dis Child* 48:646-648, 1973.

6. Saxon A, Stevens RH, Ashman RF: Regulation of immunoglobulin production in human peripheral blood leukocytes: Cellular interactions. *J Immunology* 118:1972-1976, 1977.

7. Boxer LA: Immunological function and leukocyte disorders in newborn infants. *Clin Haematol* 7:123-146, 1978.

8. Evans DG, Smith JW: Response of the young infant to active immunizations. *Br Med Bull* 19:225-229, 1963.

9. Stiehm ER: Fetal defense mechanisms. *Am J Dis Child* 129:438-443, 1975.

10. Miller ME: Current topics in host defenses of the newborn. *Adv Pediatr* 25:59-95, 1978.

11. Smith RT, Eitzman DV, Catlin ME, et al: Development of the immune response: Response of newborn and mature humans to salmonella vaccines. *Pediatrics* 33:163-183, 1964.

12. Pearlman DS: Antibody formation in infancy. *Am J Dis Child* 102:239-248, 1961.

13. Zak SJ, Good RA: Immunochemical studies of human serum globulins. *J Clin Invest* 38:579-586, 1959.

14. Hayward AR, Lawton AR: Induction of plasma cell differentiation of human fetal lymphocytes: Evidence of functional immaturity of T and B cells. *J Immunol* 119:1213-1217, 1977.

15. Morito T, Bankhurst AD, Williams RC: Studies of human cord blood and adult lymphocyte interactions with in vitro immunoglobulin production. *J Clin Invest* 64:990-995, 1979.

16. Waldmann TA, Broder S, Blaese RM, et al: Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinemia. *Lancet* 2:609-613, 1974.

17. Waldmann TA: Disorders of suppressor cells with common variable hypogammaglobulinemia and selective IgA deficiency, in Waldmann TA (ed): Disorders of suppressor immunoregulatory cells in the pathogenesis of immunodeficiency and autoimmunity. *Ann Intern Med* 88:226-238, 1978.

18. Discussion: Practical experience with poliomyelitis vaccine. *Am J Pub Health* 46:563-574, 1956.

19. McLeod DR, Wilson RJ: Status on combined vaccines, in *Poliomyelitis*. Philadelphia, JB Lippincott Co, 1960, pp 196-199.

20. Peterson JC, Christie A: Immunization in the young infant: VI. Tetanus. *Am J Dis Child* 81:518-529, 1951.

21. Welch JK, May JT: Anti-infective properties of breast milk. *J Pediatr* 94:1-9, 1979.

22. Baker CJ, Kasper DL: Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptotococcal infection. *N Engl J Med* 294:752-756, 1976.

23. Baker CJ, Kasper DL, Tager IB, et al: Quantitative determination of antibody to capsular polysaccharide in infection with type III strains of group B streptococcus. *J Clin Invest* 59:810-818, 1977.

24. Baker CJ, Edwards MS, Kasper DL: Immunogenicity of polysaccharides from type III, group B streptococcus. *J Clin Invest* 61:1107-1110, 1978.

RBC Values in Low-Birth-Weight Infants During the First Seven Weeks of Life

James A. Stockman III, MD, Frank A. Oski, MD

• **Hemoglobin, RBC mean corpuscular volume (MCV), and other RBC indices were studied in a group of 40 infants, each with a birth weight of less than 1,500 g. Results indicated that the hemoglobin level fell from 18.2 ± 2.7 g/dL at birth to a low of 9.5 ± 1.5 g/dL at 6 weeks of age. During this time, the MCV declined from 115 ± 5 fentoliters (fL) to 97 ± 5 fL and did not again rise as the hemoglobin stabilized. Although the decline in MCV may simply reflect an aging RBC population, these data raise the possibility that RBC size may in part be determined by postnatal factors independent of time from conception.**

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The determination of RBC mean corpuscular volume (MCV) in the newborn has been found to be useful in the diagnosis of several disorders, including intrauterine blood loss and α thalassemia syndromes.[1,2] Normal data for the MCV now exist for full-term infants as well as for older children.[3,4] This report provides data on the developmental changes in RBC indices in a group of infants who were born prematurely.

STUDY METHODS

Hemoglobin, RBC count, MCV, mean corpuscular hemoglobin (MCHb), and mean corpuscular hemoglobin content (MCHbC) determinations were performed by electronic counting.[5] Forty infants, each with a birth weight of less than 1,500 g (mean birth weight, 1,290 g; range, 880 to 1,495 g), were observed, with weekly determinations of RBC indices being made through the seventh week of life. All infants were of appropriate birth weight for their gestational age. The infants had no major medical or surgical complications requiring supportive care. All infants were being fed orally with commercially prepared formulas containing 15 IU α-tocopherol without added iron. Serum α-tocopherol levels, measured biweekly by the method of Quaife et al,[6] demonstrated no evidence of vitamin E deficiency. No infant had been transfused. Infants were excluded from the study if the cumulative blood losses from blood drawing exceeded 5% of the infant's estimated blood volume of 90 mL/kg. Blood for the study was obtained by the capillary technique after careful warming of the sampling site. Informed consent was obtained for this study.

RESULTS

The changes in values for hemoglobin, MCV, MCHb, MCHbC, and RBCs may be seen in the Table and in the Figure. The MCV declined from a value of 115 ± 5 fentoliters (fL) to 95 ± 5 fL by 7 weeks of age. Although it is known that the MCV obtained on the first day of life is inversely related to gestational age,[7] the decline in MCV over the first few weeks of life in this study group far exceeded that which could be accounted for by increasing age as a function of time from conception. Similar changes occurred in the MCHb while the MCHbC was relatively constant from the time of birth. The electronic counting equipment utilized for this study determined hemoglobin, MCV, and RBC counts directly while deriving values for the MCHb and MCHbC. There is no reason, however, to assume inaccuracies in the derivation of the MCHb and MCHbC.

COMMENT

The developmental changes that occur in the RBC indices of premature infants are characterized in the first few weeks of life by falling hemoglobin and RBC counts as well as by a progressive decline in the MCV and MCHb. The fall in MCV is more rapid than that observed in full-term infants.[8] Unlike the changes that

	RBC Values*				
Day	Hemoglobin (Hb), g/dL	Mean Corpuscular Volume, Fentoliters	Mean Corpuscular Hb, pg	Mean Corpuscular Hb Content, %	RBC, ×10⁶/μL
1	18.2 ± 2.7	115 ± 5	38.9 ± 1.7	33.5 ± 1.2	4.71 ± 0.75
3	16.2 ± 2.9	112 ± 4	39.0 ± 3.4	33.8 ± 1.0	4.40 ± 0.83
7	16.3 ± 2.9	110 ± 5	37.3 ± 1.8	33.9 ± 1.3	4.45 ± 0.83
14	14.5 ± 2.4	106 ± 5	36.3 ± 1.9	33.9 ± 1.0	4.10 ± 0.69
21	12.9 ± 2.0	102 ± 5	35.3 ± 2.2	34.2 ± 1.1	3.71 ± 0.59
28	10.9 ± 1.9	100 ± 5	35.1 ± 1.9	34.4 ± 1.0	3.17 ± 0.60
35	10.0 ± 1.4	98 ± 5	34.4 ± 1.5	34.5 ± 0.7	2.97 ± 0.45
42	9.5 ± 1.5	97 ± 5	32.2 ± 1.7	33.7 ± 0.9	2.92 ± 0.49
49	10.1 ± 1.7	95 ± 5	32.1 ± 1.6	33.5 ± 1.0	3.21 ± 0.59

*Values taken during first 7 weeks of life in 40 infants, each with a birth weight of less than 1,500 g. Data listed as mean ±1 SD.

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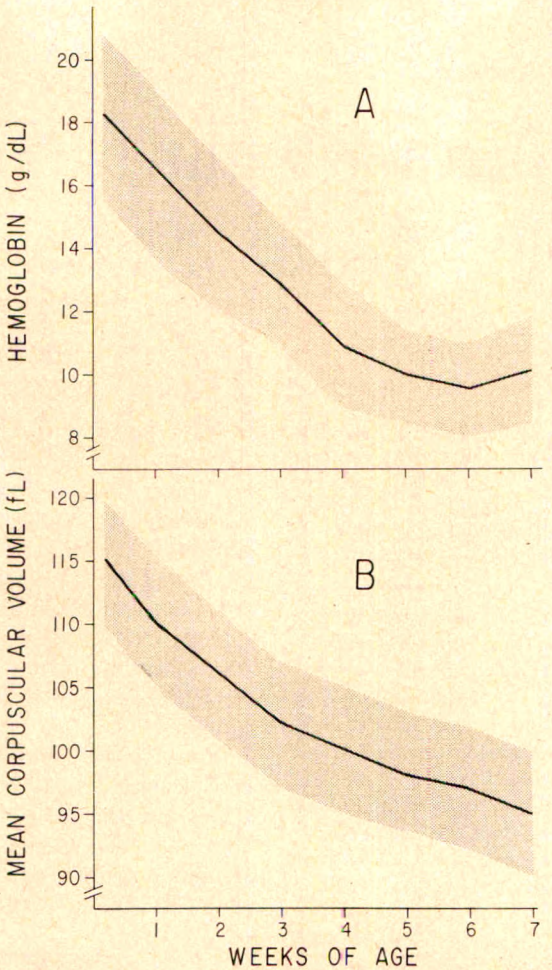

A, Relationship between postnatal age and hemoglobin concentration in group of preterm infants, each with a birth weight less than 1,500 g. B, Relationship between mean corpuscular volume and postnatal age in same group. Hatched area represents mean ± SD.

occur in fetal hemoglobin synthesis,[9] the changes in the RBC indices do not appear to be related to postconceptional age but rather to the extrauterine age.

The etiology of the decline in the MCV of these infants is not known. It is extremely unlikely that iron deficiency is in any way related to the changes that occur in the MCV during the first two months of life. Lundström et al observed no differences in the hemoglobin or MCV values at 8 weeks of age when comparing a group of infants who were born prematurely and whose diets were supplemented with 2 mg/kg/day of elemental iron with those who received no supplemental iron.[10] It should be noted that the MCV values obtained at 4 and at 7 to 8 weeks of age by the latter investigators are virtually identical to those from this study.

The decline in the MCV after birth may be the result of an aging RBC population in the face of the shortened RBC survival and the bone marrow erythroid hypoplasia that are common at this age. Normally, however, as a population of RBCs ages, there is a concomitant rise in the MCHbC of these cells, which was not observed in our series of prematurely born infants.

In addition, when in this group of 7-week-old infants the hemoglobin level no longer was observed to be falling, the MCV continued to decline. These findings suggest that the changes that occur in RBC size may represent an interesting adaptation to extrauterine life.

References

1. Schmaier AH, Maurer HM, Johnston CL, et al: Alpha thalassemia screening in neonates by mean corpuscular volume and mean corpuscular hemoglobin determination. *J Pediatr* 83:794-797, 1973.

2. Pearson HA, Diamond LK: Fetomaternal transfusion. *Am J Dis Child* 97:267-273, 1959.

3. Dallman PR, Siimes MA: Percentile curves for hemoglobin and red cell volume in infancy and childhood. *J Pediatr* 94:26-31, 1979.

4. Saarinen UM, Siimes MA: Developmental changes in the red blood counts and indices in infants with iron deficiency excluded by laboratory criteria and by continuous iron supplementation. *J Pediatr* 92:412-416, 1978.

5. *Instruction Manual for the Model 'S' Coulter Counter*, ed 5. Hialeah, Fla, Coulter Electronics, 1969.

6. Quaife ML, Scrimshaw NS, Lowry OH: A micromethod for assay of total tocopherols in blood stream. *J Biol Chem* 180:1229-1235, 1949.

7. Zaizov R, Matoth Y: Red cell values on the first postnatal day during the last 16 weeks of gestation. *Am J Hematol* 1:275-279, 1976.

8. Matoth Y, Zaizov R, Varsano I: Postnatal changes in some red cell parameters. *Acta Paediatr Scand* 60:317-323, 1971.

9. Garby L, Sjolin S, Vaille JC: Studies on erythrocyte kinetics of hemoglobin F and hemoglobin A during the first months of life. *Acta Paediatr Scand* 53:33-38, 1964.

10. Lundström U, Siimes MA, Dallman PR: At what age does iron supplementation become necessary in low-birth weight infants? *J Pediatr* 91:878-883, 1977.

Women Who Abuse Their Children

Implications for Pediatric Practice

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• Parents who abuse their children may not accept traditional therapy but may be influenced by the child's primary care physician. A comparative study of abusive and nonabusive mothers showed abusers to have lower self-concept and higher self-concept incongruence and inconsistency than nonabusers. They were also found to value authority over others more, and conformity and benevolence less, than nonabusers. Practically applied, the data lead the pediatrician to an educative and supportive role in which he or she may enhance self-esteem and lower unrealistic expectations in the course of treating the child. In addition, there seems to be a need to develop access to support groups, day care, and other avenues for the mother's personal growth. This may be done either within a pediatric practice or through liaison with community resources.

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In recent years, several studies have described the psychodynamic and demographic characteristics of child abusive individuals.[1-5] Although the data probably remain skewed by underreporting from the private sector, salient demographic factors include a preponderance of poor, female-headed households with an above-average number of children and a high rate of developmental vulnerability, such as prematurity, physical disability, or intellectual deficit in the child.[3,6,7] Abuse occurs among all socioeconomic and psychodiagnostic groups. One salient interpersonal factor, however, is that abusive parents generally maintain unrealistically high levels of expectation from their children, repeating the intense demand for and incapacity to nurture that they experienced in their own original families.[4] Their personalities are often characterized by a dependency and impulsivity that results in a role-reversed interaction with the child. The child is perceived as the unsatisfying and unsatisfiable parent of their own early lives.[1,4]

Although early identification of high-risk parents and referral to various counseling resources may represent a substantial positive outcome of such findings, less has been written on their practical application for the primary care physician in the office setting. Pediatricians must consider both the prevention of child abuse and the amelioration of the abusive impulse in the parents as an important aspect of their professional responsibility. Helfer[8] has indicated that the pediatrician "must see this responsibility as an involvement with the total family unit and not find himself caught up in the complex situation of alienating the parents in his attempt to help the child. He must make use of every talent, both his own and others, available to him, constantly keeping in mind his role as the *family* physician." Open and effective communication between physicians and parents is essential if such individuals are to trust their pediatricians enough to acknowledge the problem and accept and integrate their suggestions constructively. Often parental acknowledgment of the problem of the child abuse and neglect can come only after considerable groundwork has been laid, including successful parenting experiences based on the physician's advice. This study represents an attempt to translate objective psychological data, which confirm clinical impressions of abusive women, into practical application in the primary care pediatric setting.

METHOD

The present article is based on a comparative study of 30 abusive and 30 nonabusive mothers. The experimental group consisted of women participating in group and individual counseling at the Family Stress Center, a prevention and treatment center in Chula Vista, Calif, that accepts referrals from social service, health, and law enforcement agencies. Criteria for selection were admission of physical abuse, ranging from mild to severe nonaccidental trauma and, to minimize the effects of therapy, less than two months of participation in the program. Severity of abuse and possible presence of other abusers in the household were not assessed. Questionnaires were distributed to all abusive women entering small therapy groups. All participants returned the questionnaires anonymously at the next meeting. The group results were shared and discussed at subsequent sessions.

The control group was comprised of mothers attending the Pediatric Primary Care Center at University Hospital, San Diego. They were asked to complete the study questionnaires by the researcher during the waiting period for routine examination of children considered by the primary pediatrician to be free of suspected abuse, neglect, or major physical illness. They were told that the results would not be available unless specifically requested. Informed consent was obtained in both groups. An acknowledged limitation of the study is that the experimental group may have been more introspective and psychotherapeutically oriented than the control group.

All subjects were administered the following: a personal data sheet requesting relevant demographic information; Weedman's Self-Concept Incongruence Scale (SCIS), a 16-scale semantic differential test designed to assess positive self-concept, self-concept incongruence, and self-concept inconsistency[9]; Gordon's Survey of Interpersonal Values (SIV), a 6-scale forced-choice questionnaire that measures the most salient values involved in a person's relationships with others.[10] Both instruments have been validated with subjects demographically similar to those in the present study.

Subjects completing the SCIS are asked to rate themselves on two sets of 6-point scales, one entitled "The Way I See Myself" and the other "The Way I Would Like to Be." Scaled items included adjectives, such as friendly/unfriendly, cruel/

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kind, passive/active, and complex/simple. The authors define positive self-concept as the overall positive evaluation that a person makes of herself. Incongruence as used in this study measures the difference between the individual's actual self-perception and the way she would like to be. High scores indicate the likelihood of considerable anxiety and social maladjustment. For example, the mother who sees herself as cruel but wants to be kind might experience heightened anxiety in caretaking activities and would most likely be particularly stressed in disciplinary situations where cruel feelings might be evoked. Internal inconsistency of self-concept refers to the variability of percepts that comprise the overall positive evaluations. A tendency to endorse items, such as friendly and cruel at the same time, indicates no firm sense of personal identity and a likely behavioral pattern of impulsive and unstable interactions. Split-half reliability of the SCIS was .83. Construct validity was established by administration with the Tennessee Self-Concept Scale to 175 subjects. Correlation patterns between scores on the two tests were as follows: total positive, .934 ($P < .001$); incongruence, .824 ($P < .001$); and inconsistency, .771 ($P < .001$).[9]

The SIV consists of six scales, defined by the authors as follows:

1. Support: "being treated with understanding, receiving encouragement from other people, being treated with kindness and consideration."
2. Conformity: "doing what is socially correct, following regulations closely, doing what is accepted and proper, being conformist."
3. Recognition: "being looked up to and admired, being considered important, attracting favorable notice, achieving recognition."
4. Independence: "having the right to do whatever one wants to do, being free to make one's own decisions, being able to do things in one's own way."
5. Benevolence: "doing things for other people, sharing with others, helping the unfortunate, being generous."
6. Leadership: "being in charge of other people, having authority over others, being in a position of leadership or power."

The SIV questionnaire consists of 20 sets of three statements each, such as "to be free to do as I choose, to have others agree with me, and to make friends with the unfortunate." Subjects are asked to rate which statement is most important to them, which one is least important, and to leave one statement blank. Reliability was established by Kuder-Richardson analysis with values ranging from .71 to .86. Construct validity was established by comparison with various other self-report personality measures, such as the Allport, Vernon, Lindzey Study of Values, where correlations ranged from −.48 to .59.[10]

The data collected for the study were analyzed by two one-tailed t tests of the differences between mean scores for the experimental and control groups. The first of these procedures was used to analyze the self-concept data and the second was used to analyze the values data. Analysis of the values data also used a two-factor analysis of variance procedure to test for significant differences among the six interdependent value scales. The two factors used were the type of subject and the type of value.

RESULTS

Statistical analyses of differences between the two groups of mothers showed no significant differences in background characteristics, indicating that the women were essentially comparable in terms of demographic factors, such as age, number of marriages, number of children, age of child, educational level, race, income, occupation, and marital status (Tables 1 and 2).

Significant differences were found, however, in terms of the self-concept and interpersonal values variables. The self-concept data indicated that the women who abused their children had lower and more inconsistent self-concepts than the nonabusers, and that they experienced a greater disparity (incongruence) between the way they viewed themselves and the way they would like to be (Table 3).[11]

The values data indicated that the abusive women valued conformity and benevolence less, and authority over others more than did their nonabusive counterparts. No significant differ-

Table 1.—Demographic Characteristics

	Abusers		Nonabusers			
Variable	Mean (SD)	Range	Mean (SD)	Range	t	P
Age, yr	23.66(5.21)	17-33	24.73(4.53)	18-33	.19	NS
No. of marriages	1.43(.72)	0-3	1.20(.41)	0-2	.71	NS
No. of children	1.96(1.47)	1-6	1.46(.73)	1-3	.92	NS
Age of index child, yr	1.62(1.49)	.03-5	1.39(1.15)	.03-4	.43	NS
Education, yr	11.83(2.48)	6-18	13.17(2.74)	10-20	.39	NS

Table 2.—Demographic Characteristics

Variable	Abusers, %	Nonabusers, %	χ^2	P
Race				
White	93	83	.65	NS
Nonwhite	7	17		
Income				
< $10,000	94	80	1.31	NS
> $10,000	6	20		
Occupation				
Employed	10	23	1.08	NS
Homemaker	90	77		
Marital status				
Married	60	54	.02	NS
Unmarried	40	46		

Table 3.—Self-Concept Indices

		Abusers		Nonabusers			
Self-Concept Index	Possible Range	Mean (SD)	Actual Range	Mean (SD)	Actual Range	t	P
Incongruence	0-576	83.53(67.87)	8-317	49.93(26.92)	12-108	2.58	< .01
Total positive	12-84	58.63(10.26)	34-75	66.70(8.60)	45-84	−3.24	< .01
Internal inconsistency	0-10.80	1.69(1.50)	0-8.58	1.36(1.02)	0-3.66	1.97	< .05

ences were found in the valuing of support, recognition, and independence (Tables 4 and 5).[12]

COMMENT

Conflicts between personal values and environment conditions will, to a large extent, determine the degree to which a person experiences stress and responds to it.[10-15] Thus, the abusive mother, who finds little gratification in the performance of benevolent and nurturing tasks, may experience in exaggerated form the various psychological and economic stresses of child rearing.

A low conformist value structure associated with the rejection of rules, regulations, and cultural proprieties may prevent the abusive woman from successfully fulfilling her role as a mother. Furthermore, abusive women in this study scored significantly lower on two of the three scales (conformity and benevolence) that are characterized by high scores for the general female population.[10] As defined in this study,[10] leadership refers to the subject's need for authority and control rather than her empathy with the potential object's need for guidance. When this value is not fulfilled, power needs that are blocked in the public domain may be returned with renewed vigor to the domestic arena.[15]

Self-concept variables, as aforementioned, also influence the individual's perception of a particular experience. Thus, the abusive woman is likely to possess a negative and unstable sense of self that she seeks to modify through an idealized image of parenting that is integrated neither with her personality nor her value system.[4] The mothering experience may then become a vicious circle of failure and frustration that she tries to conceal or deny so that little corrective input is available to her.

That these are statistical data and do not negate the critical role of individual differences among abusive women is of some importance. Indeed, the physician's task of carefully observing and listening for such variations becomes even more important in view of the patient's intense need for individual attention and concern. Furthermore, the characteristics of abusive mothers described in this study reflect values and self-concept perceptions at only one point in time and may therefore be sequelae of the abusing situation rather than permanent traits. In delineating the current status of such women, however, the results guide us toward appropriate interventions in their present lives.

These findings and their relationship to the primary care physician are outlined in Table 6. The demonstrated combination of low self-concept and high self-concept incongruence makes it essential that the pediatrician carefully balances his or her supportive-

Table 4.—Two-factor Analysis of Variance of Differences Between Abusive and Nonabusive Women on the Values Indices

Source	Sum of Squares	*df*	Mean Squared	*F*	*P*
A (type subject)	2.34	1	2.34	.08	..
B (value)	6,219.12	5	1,243.82	43.31	< .01
AB	430.24	5	86.05	3.00	< .05
Within cell	9,992.90	348	28.72	...	...
Total	**16,644.60**	**359**	...	...	...

Table 5.—Values Indices

Scale	Possible Range	Abusers		Nonabusers			
		Mean (SD)	Actual Range	Mean (SD)	Actual Range	*t*	*P*
Support	0-30	19.70(4.26)	11-28	18.60(3.60)	12-27	1.05	NS
Conformity	0-30	10.23(5.17)	2-23	13.23(11.17)	0-27	−2.50	< .01
Recognition	0-30	11.70(3.42)	4-19	11.17(4.53)	5-20	.50	NS
Independence	0-30	19.06(6.15)	7-30	16.60(7.20)	2-29	1.40	NS
Benevolence	0-30	18.66(5.30)	10-28	21.73(4.62)	11-29	−2.36	< .01
Leadership	0-30	10.60(4.97)	2-21	8.57(4.10)	2-19	1.70	< .05

Table 6.—Characteristics of Abusive Mothers—Implications and Interventions

Trait	Implication	Intervention
Low self-concept	Sees self negatively; expects failure and censure; feels guilty and inadequate	Convey respect for her capacities, interests, and successes; praise when appropriate
High self-concept incongruence	Has high and unrealistic expectations of self and child; is very sensitive to criticism	Attend carefully to unrealistic expectations; praise moderately to avoid fear of reporting problems; urge and support parent education classes
High self-concept inconsistency	Has no firm sense of self; cannot convey stable image to child; may have difficulty following through consistently	Set modest and simple goals; check frequently on progress (frequent office visits and phone calls)
Low conformity	Resents rules and regulations; feels underlying hostility to authority and social demands	Solicit her opinion; develop goals together rather than as external authority
Low benevolence	Has difficulty deriving pleasure from nurturant behavior; may find child care unsatisfying	Set modest goals; encourage other activities; advocate for and support use of professional child care and relatives
High leadership	Enjoys authority over others; may seek authority exclusively over child	Encourage other activities for mother and child; educate on child's developmental need for self expression

ness and positive feedback against the danger of fostering ever higher and more unrealistic expectations in the mother. Excessive or unwarranted praise may generate even more guilt and frustration if the child fails to meet the desired standard.

Support can be most productively offered through clear acknowledgment of potential difficulties together with praise within the context of the mother's own effort. For example, an overly enthusiastic "your baby gained 2 lbs this month" focuses solely on the child and might set up an expectation that could later prove frustrating; whereas "your baby is doing fine this month, how are things going with you" praises the child but also invites the mother to share more of her feelings about what the improvement meant for her. Unrealistic expectations are mitigated by such general comments that focus on actual gains rather than ideal standards.

Anticipating potential difficulties is also important. The pediatrician may minimize the mother's sense of failure if a new approach does not work immediately by such comments as, "it may take a while before you notice changes," or "don't worry if it doesn't work right away." Although such statements may seem obvious, it is likely that the abusive mother needs such cognitive input to balance the highly idealized expectations that are reflected in the self-concept incongruence data. Parent education classes may be particularly useful here, and may even be run within the practice by a nurse practitioner, a graduate student, or another trained person.[16] This may reduce the social stigma as well as financial stress that a formal therapy referral would entail.

The inconsistency of self-concept described in this study offers the pediatrician an extremely important opportunity to help the abusive mother begin to focus on simple but consistent goals in regard to child care. Again, the physician can encourage discussion of the many changing moods the mother may experience by statements, such as, "There may be days when feeding your baby will be fun, but there will also be days when you'll have less patience and find it irritating." Setting modest goals that can be consistently worked on is critical here, and the abusive mother should be encouraged to call or visit the office when questions or problems arise. Regular office visits should be scheduled more often as well, both to monitor the child's progress and to intensively support the mother's efforts.

Abusive women in this study were as desirous of support and recognition as nonabusive mothers. This suggests that, although the needs of abusive mothers are not unlike those of other mothers, the pediatrician's support of maternal self-image and nurturing behaviors should be emphasized at each office visit.

The finding that the values of abusive women do not correlate with standard sex differences should lead the pediatrician to become familiar with community day care resources and to encourage the mother to develop interests outside the home without undue guilt. This may be done by briefly expressing interest in other than child-related aspects of her life, as well as by direct statements about the usefulness of spending some time apart from the child during the week.

The abusive mother's likely resistance to rules and regulations, and her own need for leadership, make it imperative that the pediatrician avoid an overly authoritarian posture. Advice may be indirectly offered by statements, such as "have you tried . . ." or suggested, as in "you might want to try . . .," rather than by judgmentally pronounced statements, such as "you should . . . ." Similarly, the mother's interpretation of her child's behaviors should be solicited whenever possible, so that goals are developed together. In modeling this sort of interaction, the pediatrician may also indirectly pave the way for a less authoritarian relationship between the mother and her child, with greater tolerance on her part for the child's developing need for self-assertion.

The primary care physician potentially may play a critical role in ameliorating abuse. Whereas many of these abusive women would not follow through in traditional psychotherapy, they may be accessible to the supportive role of their child's pediatrician. In addition to the medical management of the child, the physician can provide the mother with both factual information on child rearing and more realistic expectations of maternal functioning. He or she can play a role in increasing self-concept congruence by helping the mother lower her expectations and by ameliorating guilt she might feel at not being satisfied with her role. The services of a pediatric practice may be integrated with those of the community in such a way as to encourage development of the mother's need for control or power in areas outside the home. •

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References

1. Morris M, Gould R: *Role Reversal: A Necessary Concept in Dealing With the Battered Child Syndrome*. New York, Child Welfare League of America, 1963.

2. Elmer E: *Children in Jeopardy*. Pittsburgh, University of Pittsburgh Press, 1967.

3. Gil D: *Violence Against Children*. Cambridge, Mass, Harvard University Press, 1970.

4. Steele B, Pollack C: A psychiatric study of parents who abuse infants and small children, in Helfer R, Kempe CH (eds): *The Battered Child*. Chicago, University of Chicago Press, 1974, pp 89-133.

5. Paulson MJ, Schwemer GT, Bendel RB: Clinical application of the Pd, Ma and (OH) experimental MMPI scales to further understanding of abusive parents. *J Clin Psychol* 32:558-564, 1976.

6. Pelton LH: Child abuse and neglect: The myth of classlessness. *Am J Orthopsychiatry* 48:608-617, 1978.

7. Klein M, Stern L: Low birth weight and the battered child syndrome. *Am J Dis Child* 122:15-18, 1971.

8. Helfer RE: The responsibility and role of the physician, in Helfer R, Kempe CH (eds): *The Battered Child*. Chicago, University of Chicago Press, 1974, p 25.

9. Carney RE, Spielberg G, Weedman C: *Self-Concept Evaluation of Location Form: Manual*. San Diego, Carney, Weedman & Associates, 1980.

10. Gordon IV: *Survey of Interpersonal Values, Revised Manual*. Chicago, Science Research Associates, 1976.

11. Rosen B: Self-concept disturbance among mothers who abuse their children. *Psychol Rep* 43:323-326, 1978.

12. Rosen B: Interpersonal values among child abusive women. *Psychol Rep* 45:819-822, 1979.

13. Rucker R: A value-oriented framework for education and the behavioral sciences, in Laszlo E, Wilbur J (eds): *Human Values and Natural Science*. New York, Gordon and Breach, 1970, pp 81-94.

14. Maslow A: *Toward a Psychology of Being*. New York, Van Nostrand & Co, 1968.

15. Lasswell H: *Power and Personality*. New York, Norton & Co, 1948.

16. Stein MT: The providing of well-baby care within parent-infant groups. *Clin Pediatr* 16:825-828, 1977.

Disparate Cultures of Middle Ear Fluids

Results From Children With Bilateral Otitis Media

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• Cultures of middle ear fluids (MEFs) are needed to determine both efficacy of antibiotics and vaccines, and microbiologic outcome of otitis media (OM). We reviewed data on 221 children, aged 2 months to 12 years; 122 had acute otitis media (AOM), 99 had asymptomatic MEF. We included only *Streptococcus pneumoniae, Haemophilus influenzae, Branhamella catarrhalis,* and *Staphylococcus aureus* as pathogens. Of children with AOM, MEF was sterile or contained nonpathogens in both ears in 51, and one or more pathogens in 71. Of these 71, 40 had the same pathogen or pathogens in both ears; 25 patients had a pathogen in one ear and sterile fluid or only nonpathogens in the other; four patients had a different pathogen in each ear; and two patients had two pathogens in one ear and only one in the other. Of those with asymptomatic MEFs, in 80 the effusion was sterile or contained only nonpathogens in both ears, and in 19 contained one or more pathogens. Of these 19, ten had the same pathogen isolated from both ears; nine had a pathogen in one ear and sterile fluid or only nonpathogens in the other. Thus, in 31 children with AOM and nine with asymptomatic MEFs, results of cultures of MEF were different.

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The bacteriology of otitis media (OM) had been studied by needle aspiration of middle ear fluids (MEFs). Results of many such studies are remarkably consistent: *Streptococcus pneumoniae*, nontypable strains of *Haemophilus influenzae*, and group A streptococcus are the principal pathogens isolated from MEF. Isolation of one of these organisms from MEF is considered diagnostic of bacterial OM. Investigations of antimicrobial agents or vaccines rely on results of initial and subsequent cultures of MEF to evaluate microbiologic efficacy.

We noted frequent disparate results from cultures of aspirates of MEF obtained from children with bilateral OM. Such disparity may compromise microbiologic studies of OM. To determine the frequency and type of disparate results, we reviewed results of bacterial cultures of MEF from children with bilateral effusion in the middle ear.

MATERIALS AND METHODS

We reviewed results of bacterial cultures of MEF for all children with bilateral effusion of the middle ear who participated in one of three investigations conducted by us. Ninety-nine patients were included in a randomized study that compared the efficacy of sulfamethoxazole-trimethoprim or ampicillin sodium for acute OM.[1]

Forty children participated in a study to evaluate the efficacy of pneumococcal vaccine in children with recurrent episodes of acute OM (D.W. Teele, MD, J.O. Klein, MD, unpublished data, 1980) and the remaining 82 children were part of a study of the microbiology of persistent effusions of the middle ear.[2,3]

Preliminary cultures of the external auditory canal were performed using a nasopharyngeal swab. The external auditory canal was then sterilized using a 70% alcohol solution for 60 s. Alcohol was removed with a blunt-tip (Baron) aspirator and tympanocentesis was performed using a suction trap (Senturia) aspirator. The MEF was processed in the Microbiology Laboratory at Boston City Hospital. Material was inoculated onto blood, chocolate,

Table 1.—Distribution of Bacterial Isolates in 67 Children With Acute Otitis Media

Organism	No. of Isolates	Canal Alone*	Canal and Middle Ear*	Middle Ear Alone*
Haemophilus influenzae	36	0	2 (5.5)	34 (94.5)
Streptococcus pneumoniae	46	3 (6.6)	1 (2.2)	42 (91)
Branhamella catarrhalis	4	0	0	4 (100)
Staphylococcus aureus	20	15 (75)	1 (5)	4 (20)
Staph epidermidis	92	54 (58.7)	26 (28.2)	12 (13.1)
Diphtheroids	95	73 (77)	10 (10)	12 (12.6)

*Number of ears (%).

Table 2.—Results of Culture of Middle Ear Fluid (MEF) from 122 Children With Bilateral Acute Otitis Media

Results of Culture MEF1/MEF2	No. of Patients (%)
Concordant results	
Sterile/sterile	20
Sterile/nonpathogen*	17
Nonpathogen/nonpathogen	14
Subtotal	**51** (42)
Pathogen†/same pathogen	
Branhamella catarrhalis/B catarrhalis	1
Streptococcus pneumoniae/Strep pneumoniae	22
Haemophilus influenzae/H influenzae	15
H influenzae and *Strep pneumoniae*/ *H influenzae* and *Strep pneumoniae*	2
Subtotal	**40** (33)
Disparate results	
Pathogen/sterile	
B catarrhalis/sterile	2
H influenzae/sterile	4
Strep pneumoniae/sterile	5
H influenzae and *Strep pneumoniae*/sterile	2
Pathogen/nonpathogen	
H influenzae/nonpathogen	4
Strep pneumoniae/nonpathogen	6
B catarrhalis/nonpathogen	2
Pathogen/different pathogen	
Strep pneumoniae/H influenzae	4
Multiple pathogens/single pathogens	
Strep pneumoniae and *H influenzae/Strep pneumoniae*	2
Subtotal	**31** (25)
Total	**122** (100)

*Nonpathogens are bacteria other than these pathogens.
†Pathogens include *Strep pneumoniae, H influenzae, B catarrhalis,* and group A streptococcus.

Table 3.—Results of Culture of Middle Ear Effusion (MEF) in Children with Asymptomatic Bilateral Otitis Media

Results of Culture MEF1/MEF2	No. of Patients (%)
Concordant results	
Sterile/sterile	41
Nonpathogen*/nonpathogen	19
Sterile/nonpathogen	20
Subtotal	**80** (81)
Pathogen†/same pathogen	
Haemophilus influenzae/H influenzae	5
Streptococcus pneumoniae/S pneumoniae	4
Branhamella catarrhalis/B catarrhalis	1
Subtotal	**10** (10)
Disparate results	
Pathogen/sterile	
B catarrhalis/S pneumoniae/sterile	1
S pneumoniae/sterile	3
H influenzae/sterile	1
Pathogen/nonpathogen	
H influenzae/nonpathogen	3
S pneumoniae/nonpathogen	1
Pathogen/different pathogen	0
Subtotal	**9** (9)
Total	**99**

*Nonpathogens are bacteria other than these pathogens.
†Pathogens include *S pneumoniae, H influenzae, B catarrhalis,* and group A streptococcus.

and eosin methylene blue agar, and into blood and chopped meat broth. Bacterial isolates were identified by routine methods and isolates of *Strep pneumoniae,* and *H influenzae* were typed using, respectively, Danish antisera and polyvalent- and type-specific antisera obtained from the Center for Disease Control, Atlanta.

Patients were classified as symptomatic or asymptomatic based on clinical information at the time of aspiration. Those children with earache, fever, irritability, anorexia, vomiting, or diarrhea were considered to have acute OM. Those children without such symptoms were classified as having asymptomatic MEF.

RESULTS

The results of bacterial cultures of external auditory canal and MEF were available for 67 children with acute OM (Table 1). *Haemophilus influenzae, Strep pneumoniae,* and *Branhamella catarrhalis* were found in the MEF but not in the external canal in 94%, 91%, and 100% of the paired specimens. In contrast, *Staph aureus, Staph epidermidis,* and diphtheroids were usually present in the external auditory canal only or in the canal and MEF, and uncommonly in the MEF alone.

From these data we have concluded that isolation of *Strep pneumoniae, H influenzae,* or *B catarrhalis* from MEF indicates primary infection (pathogens), whereas isolation of *Staph aureus, Staph epidermidis,* or diphtheroids frequently represents contamination of MEF by organisms present in the external canal (nonpathogens).

Tympanocenteses were performed on both ears of 221 children aged 2 months through 12 years; 122 had acute OM, whereas 99 had asymptomatic MEF.

Cultures of MEF of both ears of children with acute OM had the following results: sterile MEF or the presence of nonpathogens in 51 (42%); 71 children (58%) had one or more pathogens isolated from cultures of MEF (Table 2). Forty of these children had the same pathogen or pathogens isolated from aspirates of both middle ear effusions: 22 had *Strep pneumoniae* in both MEF specimens, 15 had nontypable *H influenzae,* one patient had *B catarrhalis,* and two patients

had both *Strep pneumoniae* and nontypable *H influenzae* in each culture. In 31 (25%), the results were disparate: 13 patients had a pathogen in one ear and sterile fluid in the other, 12 patients had a pathogen in one ear and a nonpathogen in the other, four patients had a different pathogen in each ear, and two patients had nontypable *H influenzae* and *Strep pneumoniae* in one specimen of MEF and only one pathogen in the other.

Results of culture of MEF of both ears of children with asymptomatic MEF included sterile fluid or the presence of nonpathogens in 80 (81%) (Table 3). In 19 children (19%), pathogens were recovered from one or both middle ear effusions: ten children had the same pathogen isolated from aspirates of both middle ear effusions; five had nontypable *H influenzae* isolated from both middle ear specimens; four had *Strep pneumoniae* in each specimen; and one had *B catarrhalis* in each ear. In nine (9.1%), the results were disparate: five patients had a pathogen in one middle ear effusion and sterile fluid in the other, four had a pathogen isolated from one ear and a nonpathogen from the other.

Thus, analysis based on results of only one of the cultures of MEF would have been misleading in 22% of children with acute OM and 9.2% of children with asymptomatic MEF.

COMMENT

Disparity in cultures of MEF has been reported by only a few investigators. Grönroos reported 31.6% disparate results of cultures from children with bilateral OM.[4] All children had either *Strep pneumoniae, H influenzae*, or group A streptococci recovered from one MEF and sterile fluid in the other. Van Dishoeck found 19% of cultures from children with bilateral OM yielded different results.[5] The majority of children had a pathogen recovered from one ear and sterile fluid in the other. Also included were six cases in which cultures of one MEF yielded a single pathogen and the opposite MEF two pathogens. Austrian et al have recovered different serotypes of *Strep pneumoniae* in 1.5% of their cases of bilateral pneumococcal OM, but make no reference to disparate results.[6]

Our results are a minimal estimate of disparity. We chose only those bacterial species commonly recognized as pathogens: *Strep pneumoniae, H influenzae, B catarrhalis*, and *Strep pyogenes*. In 25% of children with bilateral acute OM and 9.2% of children with asymptomatic but persistent middle ear effusion, results were disparate. The frequency of disparate results observed in acute OM and asymptomatic MEF that we observed reflects the frequency of bacterial isolates in each classification. Although 25% of the children with acute OM and 9% of children with asymptomatic effusion had disparate results, if only cases of bacterial otitis are considered the frequency of disparity (43.6% vs 47.0%, respectively) is similar. These data pose a critical problem in the evaluation of efficacy of vaccines or chemotherapeutic agents used to prevent or treat disease of the middle ear. In children with bilateral disease, both ears must be evaluated, both initially and at conclusion of therapy.

Needle aspiration of MEF for microbiologic diagnosis to guide antimicrobial therapy is indicated for children with acute OM in selected circumstances: if the child is critically ill when first seen, if the child fails to respond appropriately to therapy, and for the newborn infant or child with altered host defenses who may be at risk for infection with unusual bacteria. The high incidence of different results in cultures of effusion in bilateral acute OM indicates that tympanocentesis of both ears must be performed to be certain of the microbiologic diagnosis.

Finding disparate results in a bilateral disease has not been reported in pyelonephritis, pneumonia, or diseases, such as osteomyelitis or septic arthritis, when multiple foci have been present, and may be unique to middle ear disease. Its implication may be that malfunction of the eustachian tube and reflux of nasopharyngeal secretions is the primary event in the pathophysiology of OM, and the proliferation of bacteria is secondary. The isolation of *Strep pneumoniae* and *H influenzae* from 70% of cases of bilateral OM suggests that not all bacterial species that colonize the nasopharynx are equally likely to be isolated from middle ear effusion. These pathogens may have unique properties that enable them to survive host defenses once they have gained access to the middle ear cavity.

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Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection.*

Sulfamethoxazole-trimethoprim—*Bactrim, Septra.*

References

1. Shurin PA, Pelton SI, Donner A, et al: Trimethoprim-sulfamethoxazole compared with ampicillin in the treatment of acute otitis media. *J Pediatr* 96:1081-1087, 1980.

2. Healy GB, Teele DW: The microbiology of chronic middle ear effusions in children. *Laryngoscope* 87:1472-1478, 1977.

3. Teele DW, Healy GB, Talley FP: Persistent effusions of the middle ear: Cultures for anaerobic bacteriology. *Ann Otol Rhinol Laryngol*, to be published.

4. Grönroos JA, Kortekangas AE, Ojala L, et al: The aetiology of acute middle ear infection. *Acta Otolaryngol* 58:149-158, 1964.

5. Van Dishoeck HAE, Derks ACW, Voorhorst R: Bacteriology and treatment of acute otitis media in children. *Acta Otolaryngol* 50:250-262, 1959.

6. Austrian R, Howie VM, Ploussard JH: The bacteriology of pneumococcal otitis media. *Johns Hopkins Med J* 141:104-111, 1977.

Nasal Deformities in Neonates

Their Occurrence in Those Treated With Nasal Continuous Positive Airway Pressure and Nasal Endotracheal Tubes

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• Seventy-two infants were treated with nasal continuous positive airway pressure for one day to five weeks, and nasal deformities developed in none. One hundred thirty-six infants were treated with nasotracheal tubes and eight (6%) were found to have nasal deformities. There was a strong correlation between duration of intubation and birth weight and the presence of deformities. In no infant receiving ventilation therapy for less than six days did nasal deformities develop. The incidence of nasal deformities in infants weighing less than 1,000 g was 50%, whereas in infants heavier than 1,000 g it was 2.4%. No infant had clinical symptoms suggestive of subglottic stenosis during the first year of life. The data do not support the use of routine tracheostomy in newborn infants even after prolonged intubation.

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Mechanical ventilation has dramatically improved the survival of neonates with severe respiratory distress during the past ten years. However, its use has significant complications. A number are directly related to endotracheal tubes, especially subglottic stenosis[1,2] and tracheal,[3] esophageal,[4] and pharyngeal[5] perforation. The type of endotracheal tube, whether nasal or oral, is important in determining the type of complication. Oral tubes have an increased risk of traumatic cleft palate[6,7] and gingival and dental complications,[8] whereas nasal tubes are most frequently associated with nasal deformities[9-11] and infections.[12,13] We investigated the incidence of nasal deformities and subglottic stenosis in a large series of infants treated with nasal continuous positive airway pressure (CPAP) tubes, nasal endotracheal tubes, or both.

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SUBJECTS AND METHODS

All infants treated for respiratory distress with nasal CPAP or nasotracheal intubation and ventilator therapy during the period of Oct 1, 1976 through Sept 30, 1977, were studied. Mechanical ventilation was carried out via a nasotracheal tube using a straight polyvinyl chloride (Portex) tube without a cuff. A 3.5-mm tube was used for full-term infants and a 3.0-mm tube for most premature infants. In infants weighing less than 1,250 g, a 2.5-mm tube was occasionally used. The endotracheal tubes were lubricated with xylocaine ointment before intubation. After application of benzoin to the cheeks, the tube was fixed with a strip of 1-cm adhesive tape around the neck (Fig 1). Infants requiring nasal CPAP were treated with polyvinyl chloride (Argyle) nasal CPAP tubes (small size for infants weighing $< 1,500$ g and large size for those weighing $> 1,500$ g). Nasotracheal tubes were not routinely changed. Corticosteroids and racemic epinephrine were rarely used after extubation. All infants were followed up in the newborn follow-up clinic until at least 1 year old (corrected for gestational age). During each visit, the nose was examined for evidence of nasal deformity.

RESULTS

Three hundred seventy infants required nasal CPAP, nasotracheal intubation, or both during the one-year period. One hundred seven of the infants died in the newborn intensive care unit or after discharge. Two of these had nasal deformities. Of the 263 survivors, 208 cases were followed in the newborn follow-up clinic program and constitute the basis of this study. Seventy-two infants were treated with nasal CPAP alone for a period of one day to five weeks: 67 infants for seven days or less; four infants, eight to 21 days; and one infant, five weeks. None of these infants had nasal deformities on follow-up examination.

One hundred thirty-six infants were treated with nasotracheal tubes. Fifty-seven of these infants also had nasal CPAP before or after extubation. Eight of the 136 infants (6%) were found to have nasal deformities (Table 1). There was a strong correla-

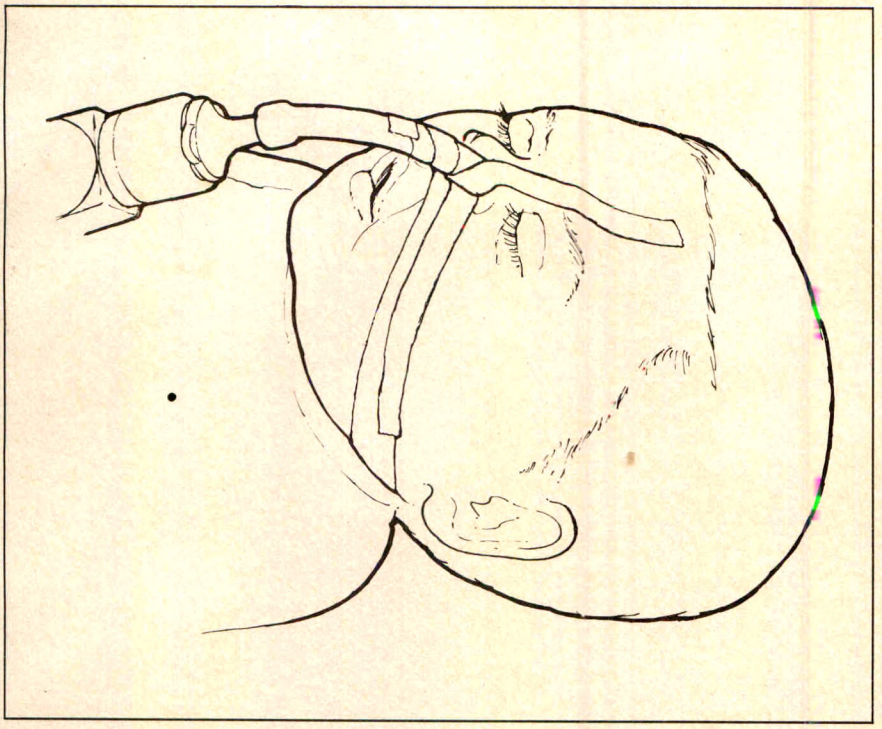

Fig 1.—Technique of taping endotracheal tube. Note direction of endotracheal tube, toward foot of patient.

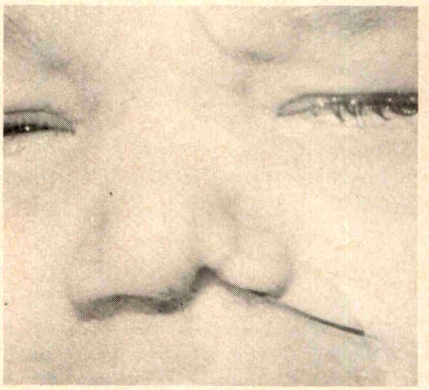

Fig 2.—Infant with esophageal atresia and tracheoesophageal fistula who had left nasotracheal intubation with permanent scar of ala nasi.

Table 1.—Eight Infants With Nasal Deformity

Patient	Gestational Age, wk	Birth Weight, g	Duration of Intubation, Days
1	28	1,000	40
2	34	2,197	7
3	37	2,400	7
4	31	880	16
5	35	2,800	6
6	28	708	11
7	28	740	38
8	27	900	13

Table 2.—Relationship of Nasal Deformities With Duration of Nasotracheal Intubation

Duration of Intubation, Days	No. of Infants	No. With Deformity (%)
1-7	119	3 (2.5)
> 7	17	5 (29)
8-15	10	2
16-21	1	1
22-28	2	0
29-42	3	2
> 42	1	0

tion with the duration of nasotracheal intubation and the presence of nasal deformities (Table 2). One hundred nineteen infants underwent nasotracheal intubation for seven days or less; three (2.5%) had nasal deformities, all of whom had been receiving ventilation therapy for six or seven days. No infant receiving ventilation therapy for less than six days had a nasal deformity. Seventeen infants received nasotracheal intubation for eight or more days, and five of these (29%) had nasal deformities. The difference between the incidence of nasal deformities in infants receiving ventilation therapy for seven days or less and in those receiving ventilation therapy for more than seven days is significant ($P < .001$).

Five of the infants with nasal deformities weighed less than 1,000 g at birth; since ten infants weighing less than 1,000 g received ventilation therapy, survived, and were followed up in the clinic during the study period, this represents a 50% incidence of nasal deformities in infants weighing less than 1,000 g. The incidence of nasal deformities in infants heavier than 1,000 g was 3:126 (2.4%). The difference is significant ($P < .001$). None of the eight infants with nasal deformities had a history of frequent otitis media in the first year of life. All of the deformities involved either scarring of the ala nasi (Fig 2), loss of cartilage of the ala nasi or nasal stenosis (Fig 3), or minimal loss of the tip of the nasal septum. In addition, no infant had clinical symptoms suggestive of subglottic stenosis and no infant required tracheostomy.

COMMENT

This report presents, to our knowledge, the largest series of infants followed up after nasotracheal intubation. It is obvious from our data that nasal deformities in our institution are correlated with very low birth weight (< 1,000 g) and prolonged nasotracheal intubation (longer than five days). In no patient ventilated for less than six days did nasal deformities develop. Most authors,[1,12] but not all,[14] have found that the duration of intubation correlates with the severity of laryngeal and nasal lesions. However, Choffat et al found that the duration of intubation did not correlate with the incidence of laryngeal

Fig 3.—Stenosis of right nostril secondary to nasotracheal intubation.

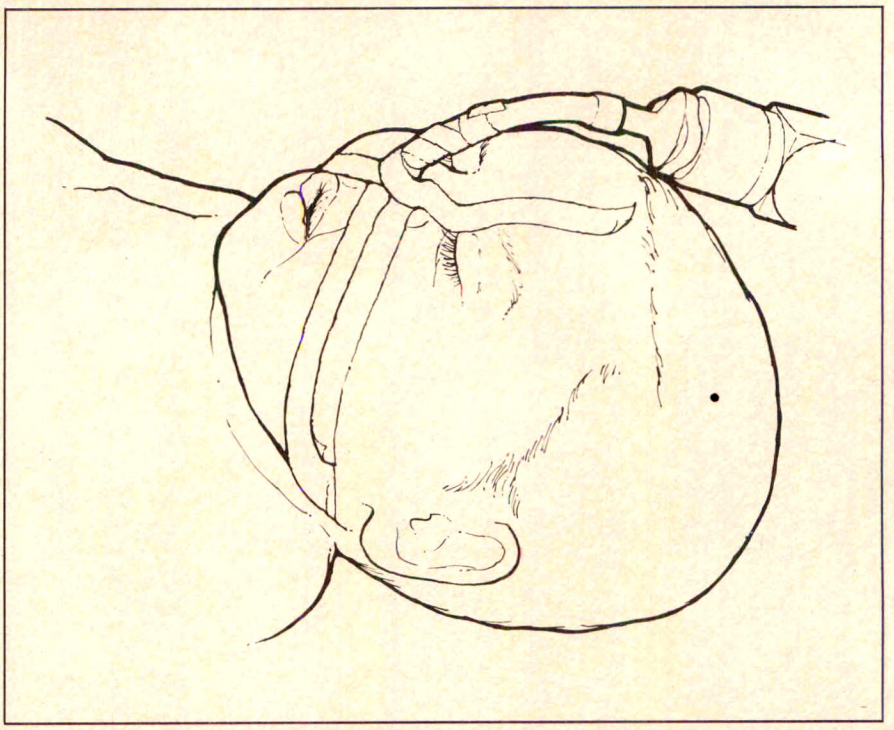

Fig 4.—Nasotracheal tube extending in cephalad direction rather than caudally. This may account for some nasal trauma with nasotracheal tubes.

and tracheal lesions in infants with endotracheal intubation,[14] and Baxter et al did not find a significant correlation between the incidence of nasal lesions and the duration of nasotracheal intubation.[11] However, none of the 49 neonates of Choffat et al weighed less than 1,000 g; only one of the patients of Baxter et al had a birth weight less than 1,000 g, and seven of their other nine patients had a birth weight of 1,000 g to 2,000 g. Thus, their data are significantly different from ours in that we had no cases of nasal deformities in infants weighing between 1,000 and 2,000 g.

The three infants in whom deformities developed with seven days or less of intubation were relatively large. This might be related to increased movement in these infants, compared with smaller infants. Whether respiratory paralysis might decrease the risk of nasal trauma is speculative. One of our three infants who received ventilation therapy, who weighed more than 2,000 g and in whom nasal trauma developed, received a paralytic agent (tubocurarine chloride), whereas the other two did not.

In the past, many authors recommended that endotracheal tubes be changed periodically, but more recently most authors recommend changing the endotracheal tube only for clinical indications, such as accidental displacement or plugging of the tube. The incidence of nasal trauma might be decreased by replacing endotracheal tubes every six to seven days. However, the trauma that may occur at the time of actual intubation—to the gingival, pharyngeal, laryngeal, and subglottic areas—may be more important than the minimal risk of nasal trauma with prolonged intubation.

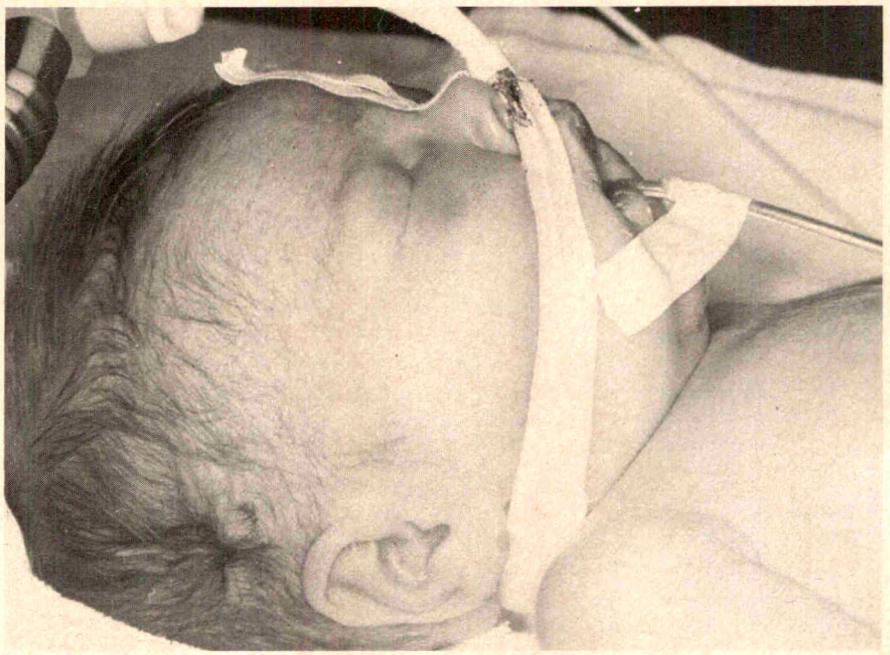

Fig 5.—Tape exerting pressure on nasal septum. This may result in loss of tip of nasal septum, especially in very low-birth-weight babies.

The low incidence of nasal lesions in infants heavier than 1,000 g (2.4%), the fact that the lesions involved only the alae and tip of the septum but not major loss of nasal septal cartilage,

and the absence of clinical problems with subglottic stenosis suggest to us that nasotracheal intubation should be continued. These infants were followed up until a corrected age of 1 year; it is, of course, possible that some cases of subglottic stenosis might occur later and, therefore, be missed by this study.

The high incidence of nasal deformities in infants weighing less than 1,000 g is disturbing. It might be possible to decrease the incidence of these lesions by fixing the tube in the direction of the infant's mouth (Fig 1) rather than in the cephalad direction (Fig 4). Allowing the tube to exit the nose in this direction might decrease the risk of trauma to the nasal alae. To do this for infants in incubators, it is preferable to bring the respirator tubes through the porthole at the foot side of the incubator rather than through the head side. In fact, maintaining the endotracheal tube in this position was first suggested by Pettett and Merenstein.[15] It might also be useful to replace the nasotracheal tube to the other nostril every seven days. Whether this would decrease the incidence of nasal trauma with prolonged intubation is, of course, speculative. Routine daily cleansing of the nostrils, with removal of crusted material and other debris, might also be helpful. Positioning the tape so that it does not exert pressure at the tip of the nasal septum (Fig 5) might prevent trauma at this site.

There is controversy over the relative advantages of nasotracheal and orotracheal intubation. A major advantage of the nasotracheal tube seems to be the decreased risk of accidental extubation. However, other authors believe that with proper precaution and fixation of orotracheal tubes, the risk of accidental extubation is no greater than with nasotracheal tubes.[16] To our knowledge, there are no data to support either side of the argument.

Because of the reports of laryngotracheal lesions with prolonged intubation in the newborn, some investigators have recently advocated the use of tracheostomy in infants requiring intubation for longer than one week.[17] However, this has not gained wide popularity and is unlikely to do so because of the disastrous results of tracheostomy in years past. One author suggested that with modern means of inserting and managing tracheostomy in neonates, the complication rate is only 8%.[17] However, their study included only 25 subjects. It is interesting that of the ten infants from 28 to 30 weeks' gestation, only one survived. Therefore, their data does not support the use of tracheostomy in very low-birth-weight infants. In fact, we know of no data that support the use of tracheostomy in infants weighing less than 1,000 g. We believe the article by Filston et al places the role of tracheostomy in infants in proper perspective, ie, its routine use in the newborn intensive care unit seems unwarranted, even after intubation for longer than seven days.[18]

References

1. Strong RM, Passy V: Endotracheal intubation: Complications in neonates. *Arch Otolaryngol* 103:329-335, 1977.
2. Joshi VV, Mandavia SG, Stern L, et al: Acute lesions induced by endotracheal intubation. *Am J Dis Child* 124:646-649, 1972.
3. Schild JP, Wuilloud A, Kollberg H, et al: Tracheal perforation as a complication of nasotracheal intubation in a neonate. *J Pediatr* 88:631-632, 1976.
4. Aplin CE, Smith M, Harrison R, et al: Acquired tracheoesophageal fistula in a premature infant. *J Pediatr* 91:983-984, 1977.
5. Touloukian RJ, Beardsley GP, Ablow RC, et al: Traumatic perforation of the pharynx in the newborn. *Pediatrics* 59:1019-1022, 1977.
6. Saunders BS, Easa D, Slaughter RJ: Acquired palatal groove in neonates: A report of two cases. *J Pediatr* 89:988-989, 1976.
7. Duke PM, Coulson JD, Santos JI, et al: Cleft palate associated with prolonged orotracheal intubation in infancy. *J Pediatr* 89:990-991, 1976.
8. Boice JB, Krous HF, Foley JM: Gingival and dental complications of orotracheal intubation. *JAMA* 236:957-958, 1976.
9. Sinclair JC: Problems associated with prolonged nasotracheal intubation. *Problems of Neonatal Intensive Care Units*. Columbus, Ohio, Ross Laboratories, 1969, pp 69-80.
10. Jung AL, Thomas GK: Stricture of the nasal vestibule: A complication of nasotracheal intubation in newborn infants. *J Pediatr* 85:412-414, 1974.
11. Baxter RJ, Johnson JD, Goetzman BW, et al: Cosmetic nasal deformities complicating prolonged nasotracheal intubation in critically ill newborn infants. *Pediatrics* 55:884-887, 1975.
12. Verhoog-Bloembergen MPJ, Leader GL: Long-term nasotracheal intubation. *Int Anesth Clin* 12:241-257, 1974.
13. Berry FA Jr, Blankenbaker WL, Ball CG: A comparison of bacteremia occurring with nasotracheal and orotracheal intubation. *Anesth Analg* 52:873-876, 1973.
14. Choffat JM, Goumaz CF, Guex JC: Laryngotracheal damage after prolonged intubation in the newborn infant, in Stetson JB, Swyer PR (ed): *Neonatal Intensive Care*. St Louis, Warren H Green Inc, 1976, pp 253-270.
15. Pettett G, Merenstein GB: Nasal erosion with nasotracheal intubation. *J Pediatr* 87:149-150, 1975.
16. Gregory GA: Respiratory care of newborn infants. *Pediatr Clin North Am* 19:311-324, 1971.
17. Heroy JH, MacDonald MG, Mazzi E, et al: Airway management in the premature infant. *Ann Otol Rhinol Laryngol* 87:1-7, 1978.
18. Filston HC, Johnson DG, Crumrine RS: Infant tracheostomy: A new look with a solution to the difficult cannulation problem. *Am J Dis Child* 132:1172-1176, 1978.

Fluid Administration and Bronchopulmonary Dysplasia

The Lack of an Association

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• The fluid intake of 38 surviving infants with severe respiratory distress syndrome was evaluated. There were no substantial differences in fluid administration between those in whom bronchopulmonary dysplasia (BPD) developed and those in whom it did not. The factors that were associated with the development of BPD were the degree of prematurity, patent ductus arteriosus, pulmonary air leak, exposure to high concentrations of oxygen, and use of ventilation at faster rates.

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A recent report[1] suggested that there is an association between fluid intake during the first five days of life and the development of bronchopulmonary dysplaisa (BPD). To address the possibility of such an association, we examined data from infants who were treated with mechanical ventilation for respiratory distress syndrome (RDS).

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PATIENTS AND METHODS

We recorded the noncolloid fluid intake (the sum of parenteral and enteral fluid administered), amount of blood products administered, daily weight, and use of phototherapy for all 69 infants with severe RDS who were admitted to our nursery during the 12-month period ending in December 1978. Fluid intake was expressed as milliliters per kilogram per day using the infant's weight at the beginning of the 24-hour period. Changes in weight were expressed as percent of birth weight.

Ventilation of all patients was supported with a time-cycled, pressure-limited ventilator that used unwarmed, humidified gas at relatively low pressures and rates as well as either a 1:2 or a 2:1 inspiratory to expiratory (I/E) ratio. They received care in servocontrolled incubators, with heat shields in the incubators for those infants weighing less than 1,200 g.

The diagnosis of bronchopulmonary dysplasia was made in patients in whom the typical roentgenographic findings[2] were made and who had a continuing supplemental oxygen requirement at 1 month of age. Pulmonary air leak was defined by roentgenographic evidence of pulmonary interstitial emphysema, pneumomediastinum, or pneumothorax. Patent ductus arteriosus (PDA) was diagnosed on the basis of the classical murmur in association with collapsing pulses; a marked PDA was one that was symptomatic to the degree that the clinical staff initiated therapy with furosemide and/or digoxin for treatment of congestive heart failure.

For purposes of analysis, the patients were divided into two groups. Group 1 comprised those patients with RDS in whom BPD did not develop, while group 2 comprised those with RDS in whom BPD did develop. χ^2 test, Student's t test, and Wilcoxon's rank sum test were used to evaluate statistical significance. A $P < .05$ defined statistical significance.

RESULTS

Of the 69 patients entered into the study, 39 lived longer than 28 days. The data from 38 of these survivors were analyzed. The patient excluded from the analysis was transferred to another nursery at 5 days of age when he no longer required mechanical ventilation. There were 29 patients in group 1 and nine in group 2. Patients in group 2 had significantly lower birth weights ($P < .02$, Wilcoxon's rank sum test) and gestational ages ($P < .01$) (Table 1). No significant differences existed between the groups

for place of birth (inborn vs outborn), sex, asphyxia, and the use of phototherapy. At the time of entry into the study, the severity of the RDS was similar for the groups as indicated by clinical findings, chest roentgenograms, and alveolar-arterial oxygen difference values taken at 6 hours of age (Table 1).

There were no significant differences in fluid intake or in weight gain between the groups (Table 2). Since the occurrence of BPD was more common in lower-birth-weight infants, we compared fluid intake for infants weighing less than 1,800 g in each group. The mean daily noncolloid intake for these lower-birth-weight infants in group 1 (n = 15) was 111 mL/kg/day; for group 2 infants weighing less than 1,800 g (n = 8), it was 114 mL/kg/day during the first 7 days of age. Mean total fluid intake for lower-birth-weight infants of group 1 was 115 mL/kg/day, and for group 2 infants weighing less than 1,800 g it was 123 mL/kg/day during the first week of age.

However, there were differences between the groups in the incidence of PDA and pulmonary air leak and in the ventilator settings (Table 1). Four patients in group 2 and one in group 1 had significant PDA ($P < .01$). Pulmonary air leak occurred four times in group 2 and three times in group 1 ($P < .05$). Infants in whom BPD developed were exposed to 101 ± 17 hours (mean ± SEM) of fraction of inspired oxygen greater than 0.40 while receiving mechanical ventilation during the first week compared with 21.4 ± 4.9 hours for group 1 ($P < .001$). Those in whom BPD developed were treated with ventilator rates of more than 25 cycles/min for 53.0 ± 15.5 hours compared with 6.4 ± 2.1 hours for group 1 ($P < .01$). There were no significant differences between the groups in end-expiratory pressures and inspiratory pressures used. The different I/E ratios did not influence the development of BPD.

COMMENT

Many factors have been associated with the development of BPD. These include prolonged exposure to high concentrations of oxygen,[2] endotra-

Table 1.—Birth Factors, Morbidity, and Ventilator Settings

	Group 1 (n = 29)	Group 2 (n = 9)	Statistical Significance
Birth weight, g			
Range	1,180-3,490	800-3,740	$P < .02$*
Median	1,660	1,160	
Gestational age, wk			
Range	29-36	25-38	$P < .01$*
Median	32	30	
Sex, M/F	15/14	6/3	NS†
Route of delivery, vaginal/cesarean section	20/9	6/3	NS†
Place of birth, inborn/outborn	20/9	6/3	NS†
Asphyxia‡	10	4	NS†
Phototherapy	6	4	NS†
Inspiratory-expiratory ratio, 1:2/2:1	16/13	5/4	NS†
Alveolar-arterial oxygen difference at 6 hr of age, mm Hg	224 ± 19§	212 ± 39	NS‖
Pulmonary air leak	3	4	$P < .05$†
Significant patent ductus arteriosus	1	4	$P < .01$†
Hours ventilated during first week			
Forced inspiratory oxygen > 0.40	21.4 ± 4.9§	101 ± 17	$P < .001$‖
Rate > 25 cycles/min	6.4 ± 2.1	53.0 ± 15.5	$P < .01$‖
End-expiratory pressure > 4 cm H_2O	8.1 ± 3.9	12.1 ± 7.3	NS‖
Inspiratory pressure > 30 cm H_2O	3.3 ± 3.0	7.8 ± 6.6	NS‖

*Wilcoxon's rank sum test.
†χ^2 test.
‡Cord blood pH < 7.20 or one-minute Apgar score < 6.
§Mean ± SEM.
‖Student's t test.

Table 2.—Fluid Intake and Weight Change During First 7 Days of Age

	Group 1 (n = 29)	Group 2 (n = 9)
Fluid intake		
Noncolloid fluid,* mL/kg/day, on day		
1	65.3 ± 3.0†	67.8 ± 5.0
2	75.1 ± 2.5	77.6 ± 8.9
3	97.0 ± 6.1	101 ± 14.4
4	114 ± 5.8	130 ± 17
5	136 ± 7.4	136 ± 9.8
6	137 ± 6.5	149 ± 13
7	147 ± 6.0	145 ± 19
Daily mean	110 ± 3.3	115 ± 9.5
Total fluid,‡ mL/kg/day		
Daily mean	114 ± 3.3	123 ± 9.7
Weight change, % birth weight on day		
2	−0.1 ± 0.4	+1.3 ± 1.5
3	−3.7 ± 0.8	−1.6 ± 2.7
4	−5.1 ± 0.7	−4.4 ± 2.3
5	−6.1 ± 0.8	−6.6 ± 1.9
6	−7.2 ± 0.8	−6.4 ± 1.6
7	−7.5 ± 0.7	−6.2 ± 2.2

*Parenteral plus enteral intake.
†Mean ± SEM.
‡Parenteral and enteral intake plus blood products.

cheal intubation,[3] exposure to high, peak inspiratory pressure during mechanical ventilation,[4] PDA,[5] and decreased availability of antioxidant substances.[6] Our patients in whom BPD developed had longer exposure to high concentrations of oxygen and had higher incidences of PDA and pulmonary air leak than patients in whom BPD did not develop.

Recently, Brown et al[1] reported that infants in whom BPD developed had received considerably more fluid during the first five days of life compared with those in whom BPD did not develop. They treated 43 infants with ventilation, in seven of whom BPD developed. These authors suggested that the increased fluid intake may be "edemagenic" and may contribute to the development of BPD. We did not find a significant increase in fluid administration to those patients in whom BPD developed. Our patients with BPD had a mean daily total fluid intake of 123 ± 10 mL/kg/day compared with 114 ± 3.3 mL/kg/day for the other group. Fluid retention, despite conservative fluid administration in group 2, is unlikely since there were no significant differences in weight gain between the groups (Table 2). It is difficult to resolve the discrepancies between our study and that of Brown et al.[1] There may have been basic differences in patient populations since all of the patients in the study of Brown et al who had BPD also had PDA, while only four of our nine patients with BPD also had PDA. The conclusions of both studies are based on small numbers of patients with BPD, and data from more patients are required to define with certainty the role of fluid administration in the development of BPD.

It would appear that if fluids are administered at conservative rates (110 to 125 mL/kg/day), factors other than fluid intake are more important in the development of BPD. In our patients with severe RDS who were receiving mechanical ventilation, these factors were the degree of prematurity, pulmonary air leak, PDA, prolonged exposure to high concentrations of oxygen, and ventilation at faster rates.

References

1. Brown ER, Stark A, Sosenko I, et al: Bronchopulmonary dysplasia: Possible relationships to pulmonary edema. *J Pediatr* 92:982-984, 1978.
2. Northway WH Jr, Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline membrane disease. *N Engl J Med* 276:357-368, 1967.
3. Edwards DK, Dyer WM, Northway WH Jr: Twelve years' experience with bronchopulmonary dysplasia. *Pediatrics* 59:839-846, 1977.
4. Reynolds EOR, Taghizadeh A: Improved prognosis of infants mechanically ventilated for hyaline membrane disease. *Arch Dis Child* 49:505-515, 1974.
5. Gay JH, Daily WJR, Meyer BHP, et al: Ligation of the patent ductus arteriosus in premature infants: Report of 45 cases. *J Pediatr Surg* 8:677-683, 1973.
6. Ehrenkranz RA, Bonta BW, Ablow RC, et al: Amelioration of bronchopulmonary dysplasia after vitamin E administration. *N Engl J Med* 299:564-569, 1978.

Boy 'Carrying in' Bottles in Glass Works, WVa

Lewis W. Hine 1911 From the International Museum of Photography, Rochester, NY

Hyperfunctioning Thyroid Nodules in Children

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• We studied two cases of hyperfunctioning thyroid nodules in children. A 9-year-old girl and an 11-year-old girl had thyroid masses in otherwise nonpalpable thyroid glands. Scintiscan showed hyperfunctioning thyroid nodules. The former patient had elevated values for T_4 and T_3, and plasma thyrotropin (TSH) level failed to respond to stimulation with thyrotropin releasing hormone (TRH), whereas the latter patient had normal values for T_4 and T_3 and plasma TSH response to TRH was normal. After the surgical removal of nodules, scintiscan exhibited radioactivity in the contralateral lobe of the thyroid gland in the former and in the ectopic thyroid tissue in the latter. Results of microscopic examinations of thyroid nodules were consistent with adenomatous goiter.

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The hyperfunctioning thyroid nodule is very rare in children, although not unusual in adults. To our knowledge, only nine children with this disease have been reported in the literature.[1-6] We studied two patients with hyperfunctioning thyroid nodules and reviewed briefly nine recorded cases of this disorder in childhood.

REPORT OF CASES

CASE 1.—A 9-year-old girl was admitted to the hospital because of a swelling in her neck. On admission, a firm 2.5 × 3.5-cm nontender nodule was felt in the right lobe of the thyroid. There were no palpable regional lymph nodes. Pulse rate was 120 beats per minute and blood pressure was 128/80 mm Hg. No eye signs of Graves' disease were noted. There were no tremor, palpitation, sleep disturbance, excessive sweating, or other symptoms of thyroid dysfunction.

Results of thyroid function studies showed elevated plasma triiodothyronine (T_3) and thyroxine (T_4) levels, which were 246 ng/dL and 16.2 μg/dL, respectively (Table 1). The thyroid uptake with ^{131}I was 31% after 24 hours. The thyroid scan showed all radioactivity confined to the palpable nodule (Figure). The patient was stimulated with 10 units of bovine thyrotropin (TSH) given intramuscularly on three consecutive days. The thyroidal ^{131}I uptake at 24 hours rose to 59.8% and a slight additional uptake was demonstrated in the left lobe, indicating the existence of the extranodular suppressed tissue of the thyroid (Figure). After the oral administration of 75 μg of T_3 for eight days, the thyroid uptake with ^{131}I was 26.2% at 24 hours. Basal plasma TSH concentration was undetectable and plasma TSH level failed to increase after the intravenous administration of thyrotropin releasing hormone (TRH) in a dose of 5 μg/kg of body weight. Antibodies to thyroid microsomes or thyroglobulin were not detected.

Because of clinical and laboratory evidence of a hyperfunctioning thyroid nodule, a right thyroid lobectomy was performed. Microscopic examination of nodule was consistent with adenomatous goiter.

After operation, the patient was transiently hypothyroid, with a serum T_3 level

Table 1.—Thyroid Function Studies

Source	Radioiodine Uptake at 24 hr		T_3, ng/dL	T_4, μg/dL	TSH*		Antibodies	
	Baseline, %	After T_3 Administration			Baseline, μU/mL	After TRH Administration	AMA	ATA
Rosenbloom[1]	...	...	...	5.7	...	...	...	...
Pompa et al[2]	22	Not suppressed	405	10.7	...	...	...	...
Rosenbloom and Person[3]	...	...	...	7.2	...	...	...	...
Taylor[4]	...	...	650	17.2	9.6	...	...	...
Hopwood et al[5]	16.3	Slightly suppressed	200	5.5	< 2.0	...	ND	ND
Hopwood et al[5]	37.8	Not suppressed	270	6.5	< 1.5	...	ND	ND
Hopwood et al[5]	...	...	90	7.4	< 2.0	...	...	...
Hopwood et al[5]	20.2	Not suppressed	170	4.9	4.5	...	...	...
Granoff and Hershman[6]	...	...	345	18.0	< 0.3	Not increased	ND	ND
Present study	31.0	Not suppressed	246	16.2	ND	Not increased	ND	ND
Present study	33.3	Suppressed	176	7.9	2.5	Increased	ND	ND
Normal range	15-44	...	80-180	5-14	< 10.0	...	...	...

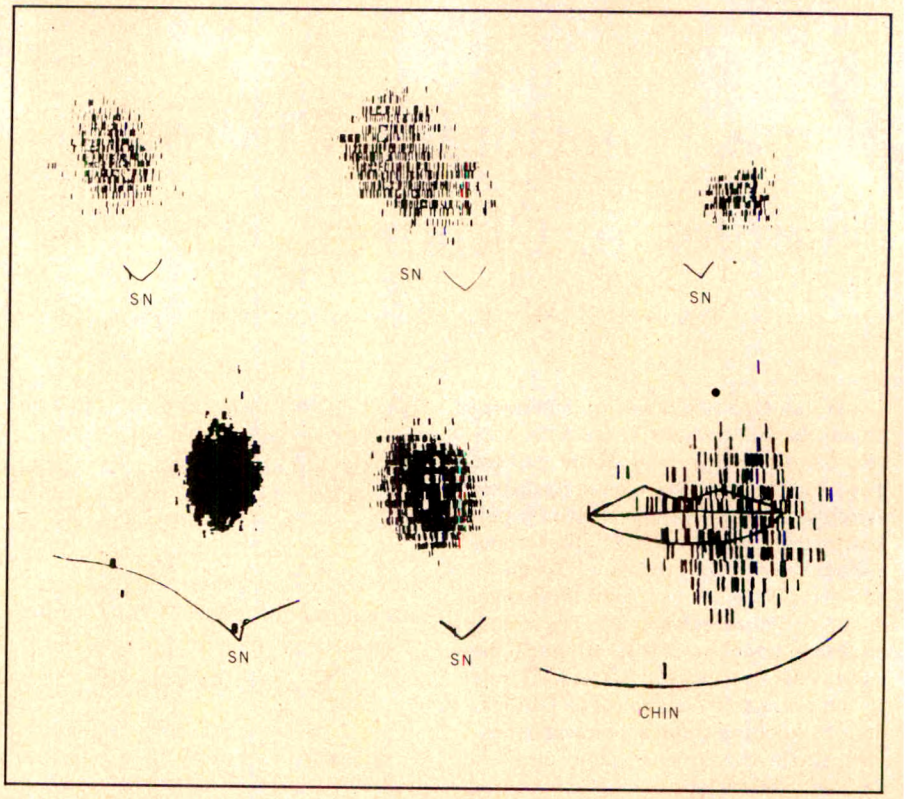
*TSH indicates thyrotropin; TRH, thyrotropin releasing hormone; AMA, antimicrosomal antibody; ATA, antithyroglobulin antibody; and ND, not detected.

of 90 ng/dL and a T_4 level of 4.2 μg/dL. Four months later, however, the patient was euthyroid chemically, with a T_3 level of 176 ng/dL and a T_4 level of 12.2 μg/dL. The thyroid scan revealed radioactivity in the left lobe of the thyroid. (Figure).

CASE 2.—An 11-year-old girl was admitted to the hospital because of a mass in the right side of the neck. She had been followed up every six months at another hospital for a small ventricular septal defect, when her pediatrician had noted a right thyroid mass.

On admission, a very firm 3 × 4-cm nontender mass was present in the area of the right lobe of the thyroid. Regional lymph nodes were not palpable. Pulse rate was 84 beats per minute and blood pressure was 100/60 mm Hg. There were no signs and symptoms suggestive of hyper- or hypothyroidism. Thyroid function studies showed normal plasma TSH, T_3, and T_4 levels of 2.5 μU/mL, 176 ng/dL, and 7.9 μg/dL (Table 1). The thyroid uptake with ^{131}I was 33.3% at 24 hours. The thyroid scan showed all radioactivity restricted to the nodule (Figure). After three days of TSH stimulation (10 units, twice a day), the 24-hour thyroidal ^{131}I uptake rose to 67.1%, and again the scintiscan showed radioactivity localized in the nodule; no function was visible in the extranodular thyroid tissue (Figure). After the administration of 75 μg of T_3 for seven days, the thyroidal ^{131}I uptake at 24 hours fell to 6.3% and there was no change in distribution of radioactivity on scintiscan. Plasma TSH concentration rose from 2.5 to 18.7 μU/mL after TRH stimulation. Antibodies against thyroid microsomes or thyroglobulin were not detected. Owing to the inordinate firmness of the nodule to palpation, surgical removal of nodule was performed. During the operation, the left lobe was found to be absent. Microscopic examination was compatible with adenomatous goiter.

Two weeks after surgery, the patient was chemically hypothyroid, with a T_3 level of 85 ng/dL, a T_4 level of 2.3 μg/dL, and a TSH level of 116 μU/mL, and the thyroid scan showed radioactivity in the mouth, indicating the presence of ectopic thyroid tissue (Figure). The patient has now been given 125 μg of thyroxine daily and carefully followed up. To date her health has remained satisfactory.



Radioiodine scintigrams of cases 1 and 2. Upper left, before therapy in case 1; upper middle, after thyrotropin (TSH) stimulation in case 1; upper right, ten days after operation in case 1. Lower left, before therapy in case 2; lower middle, after TSH stimulation in case 2; lower right, 14 days after operation in case 2. SN indicates suprasternal notch.

COMMENT

The hyperfunctioning thyroid nodule is uncommon in childhood. Case 1 represents a typical case of this disease. The thyroid scan revealed a "hot" nodule (defined as an area with increased uptake of radioactive isotope) independent of TSH control, as evidenced by failure of suppression of thyroidal ^{131}I uptake with T_3. Case 2, however, shows some unusual features. Although the thyroid scan demonstrated a hot nodule, the thyroid uptake of ^{131}I was suppressed by T_3, and plasma TSH levels significantly increased in response to TRH stimulation. These data were not compatible with those observed in most of adult patients with hyperfunctioning thyroid nodules.[7,8] Nevertheless, evidence of thyroid function was noted in the ectopic thyroid tissue on follow-up scintigram after surgical removal of the nodule. This finding is diagnostic of a hyperfunctioning thyroid nodule. Thus, it is tempting to explain the conflicting data by postulating incomplete TSH-dependence for the hot nodule, suppression of function in ectopic thyroid tissue prior to treatment, and congenital absence of the contralateral thyroid lobe. To our knowledge, only one patient similar to case 2 has been described in the literature, by Molnar et al.[9]

The clinical features of the hyperfunctioning thyroid nodule include swelling or mass in the neck and symptoms and signs of hyperthyroidism. In all of 11 children reported to date[1-6] with hyperfunctioning thyroid nodules, the initial complaint was only either a thyroid mass or a swelling in the neck.

The clinical picture of hyperthyroidism differs from that seen in Graves' disease. Symptoms and signs are usually mild and cardiovascular manifestations, such as tachycardia and wide pulse pressure, are often the only indication of hyperthyroidism. Eye signs, neuromuscular features, and gastrointestinal symptoms are usually absent, in contrast to their association with Graves' disease.

The incidence of association of hyperthyroidism with hyperfunctioning thyroid nodule seems high in children, as compared to adults. Eight of the 11 children with this disorder were found to be hyperthyroid, as shown in Table 2, whereas collating five series gives an incidence of hyperthyroidism

Table 2.—Clinical Data

Source	Patient Age, yr/ Sex	Clinical State	Site of Nodule	Size of Nodule	Abnormality
Rosenbloom[1]	9/F	Euthyroid	L	3 × 2	. . .
Pompa et al[2]	6/F	Hyperthyroid	L	4 × 4	Adenoma
Rosenbloom and Person[3]	4/F	Hyperthyroid	L	. . .	Colloid goiter
Taylor[4]	11/F	Hyperthyroid	R	3.5 × 2.5	Adenoma
Hopwood et al[5]	15/F	Hyperthyroid	L	1 × 2	Adenomatous goiter
Hopwood et al[5]	15/F	Hyperthyroid	R	2.5 × 1.5	Papillary adenocarcinoma
Hopwood et al[5]	14/F	Euthyroid	L	4 × 4	Adenomatous goiter
Hopwood et al[5]	11/F	Hyperthyroid	R	2 × 2	Thyroid hyperplasia
Granoff and Hershman[6]	6/F	Hyperthyroid	L	3 × 2.5	Adenoma
Present study	9/F	Hyperthyroid	R	2.5 × 3.5	Adenomatous goiter
Present study	11/F	Euthyroid	R	4 × 4	Adenomatous goiter

of 48% in a total of 123 cases of hyperfunctioning thyroid nodules in adult patients.[9-13]

Note that all of the children listed in Table 2 are girls. This indicates a definite predominance in girls as well as in women.[7,9,12] Although pathologic examinations of thyroid nodules reveal adenoma in the majority of adult patients,[9] adenoma is much less frequently identified in children, as demonstrated in Table 2.

Regarding thyroid function in adult patients with hyperfunctioning thyroid nodules, considerable information is available in the literature.[7-9,11-13] Thyroid function studies in children are given in Table 1.

Patients with clinical features of hyperthyroidism usually show significant elevations in serum T_3 and T_4 concentrations. A preferential elevation of serum T_3 (T_3-toxicosis) also often occurs. In addition, serum TSH usually fails to respond to TRH stimulation and the thyroidal ^{131}I uptake is not suppressible by exogenous administration of thyroid hormone, regardless of whether the patient is euthyroid or hyperthyroid. Although the positive correlation between the size of thyroid nodule and the presence of hyperthyroidism has been reported in adult patients,[9,12] such a correlation is not found in children.

Since the patients present most frequently with a thyroid mass or a swelling in the neck, the differential diagnosis includes acute suppurative thyroiditis, subacute thyroiditis, Hashimoto's thyroiditis, thyroid carcinoma, thyroid cyst, benign adenoma, and thyroid dysgenesis.

The physical examination of the thyroid gland and surrounding lymph nodes, thyroid function studies and the thyroid scan may be sufficient for diagnosis. Among these, the thyroid scan is especially useful as a diagnostic tool. The thyroid scintigram always demonstrates a hot nodule with no visible uptake in the remainder of the thyroid. It is of importance to remember that although function in a thyroid nodule largely excludes a malignant disease, there have been some reports of carcinoma in hyperfunctioning thyroid nodules[5,14,15] and that 3% to 4% of the patients with Hashimoto's thyroiditis have functioning nodules.[16] The hemiagenesis of the thyroid gland may simulate a unilaterally functioning nodule.[5]

Treatment consists of surgical removal of the nodule if the patient is hyperthyroid or if there are some clinical findings suggestive of thyroid carcinoma, such as (1) rapid growth of the nodules, (2) enlargement of adjacent lymph nodes, (3) hoarseness or vocal cord paralysis, (4) rock-like hardness, and (5) history of prior radiation therapy to the neck.

Antithyroid drug therapy is considered only for short-term management. If the patient remains euthyroid, follow-up may be desirable. Studies of the natural history of hyperfunctioning thyroid nodule indicate a rare progression to thyrotoxicosis, but not to malignancy.[11,12,17]

References

1. Rosenbloom AL: Functioning solitary nodule of the thyroid in a child. *J Pediatr* 82:491-493, 1973.
2. Pompa BH, Cloutier MD, Hayles AB: Thyroid nodule producing T_3 toxicosis in a child. *Mayo Clin Proc* 48:273-275, 1973.
3. Rosenbloom AL, Person KK: Nodular toxic goiter (Plummer's disease) in a child. *J Pediatr* 84:104-107, 1974.
4. Taylor HC: Solitary hyperfunctioning thyroid adenoma in a child. *JAMA* 234:1253-1255, 1975.
5. Hopwood NJ, Carroll RG, Kenny FM, et al: Functioning thyroid masses in childhood and adolescence. *J Pediatr* 89:710-718, 1976.
6. Granoff AB, Hershman JM: Suppression of pituitary TSH in a child with a hyperfunctioning thyroid nodule. *J Pediatr* 90:83-85, 1977.
7. Karlberg BE: Thyroid nodule autonomy: Its demonstration by the thyrotropin releasing hormone (TRH) stimulation test. *Acta Endocrinol* 73:689-699, 1973.
8. Ridgway EC, Weintraub BD, Cevallos JL, et al: Suppression of pituitary TSH secretion in the patient with a hyperfunctioning thyroid nodule. *J Clin Invest* 52:2783-2792, 1973.
9. Molnar GD, Wilber RD, Lee RE, et al: On the hyperfunctioning solitary thyroid nodule. *Mayo Clin Proc* 40:665-684, 1965.
10. Sheline GE, McCormack K: Solitary hyperfunctioning thyroid nodules. *J Clin Endocrinol* 20:1404-1408, 1960.
11. Silverstein GE, Burke G, Cogan R: The natural history of the autonomous hyperfunctioning thyroid nodule. *Ann Intern Med* 67:539-548, 1967.
12. Blum M, Shenkman L, Hollander CS: The autonomous nodule of the thyroid: Correlation of patient age, nodule size and functional status. *Am J Med Sci* 269:43-50, 1975.
13. Marden P, Facer P, Acosta M, et al: Serum triiodothyronine in solitary autonomous nodules of the thyroid. *Clin Endocrinol* 4:327-330, 1975.
14. Becker FO Economou PG, Schwartz TB: The occurrence of carcinoma in "hot" thyroid nodules. *Ann Intern Med* 58:877-882, 1963.
15. Meier DA, Hamburger JI: An autonomously functioning thyroid nodule, cancer and prior radiation. *Arch Surg* 103:759-761, 1971.
16. Fisher DA, Oddie TH, Johnson DE, et al: The diagnosis of Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 40:795-801, 1975.
17. Landgarten S, Spencer RP: A study of the natural history of "hot" thyroid nodules. *Yale J Biol Med* 46:259-263, 1973.

Nosocomial Transmission of Bacteriophage Type 7/11/12 Group B Streptococci in a Special Care Nursery

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• Two premature infants in a special care nursery acquired late-onset group B streptococcal (GBS) sepsis within a 24-hour period. The infecting strains were serotype III organisms with bacteriophage type 7/11/12. Cultures of the mothers of the two affected infants were negative for GBS, implying nosocomial acquisition of infection. Although 32% of nursery personnel had mucosal carriage of GBS, none of the seven isolates of GBS type III was the same bacteriophage type as the two infecting strains. Of the other infants hospitalized in the nursery, five were asymptomatically colonized with GBS. These infants were in bassinets adjacent to the affected infants; all five of their isolates were identical to the two infecting strains. We conclude that infant-to-infant transmission may result in nosocomial late-onset GBS septicemia.

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Vertical transmission from the maternal genital tract during labor is recognized as the principal mode of perinatal acquisition of group B streptococci (GBS). However, only about 1% of infants born to colonized mothers manifest "early-onset" septicemia.[1] The association of early-onset invasive disease with perinatal complications[2] and diffuse pneumonia[3] support the concept of intrapartum amniotic fluid infection as a major pathogenic determinant. In contrast, the transmission and pathogenetic mechanisms of "late-onset" GBS septicemia have not been defined. Late-onset disease could result from postnatal colonization by GBS strains of nonmaternal origin, a hypothesis that has drawn attention to the phenomenon of nosocomial colonization in the neonatal nursery setting.

In several recent reports of hospital-acquired GBS colonization of normal newborns,[4-6] personnel with mucosal carriage have been identified as a major reservoir. However, owing to difficulties in exact identification of GBS strains, it has not been possible to document the epidemiologic significance of this reservoir, nor the contribution of horizontal transmission from infant to infant.

The simultaneous occurrence of late-onset GBS sepsis in two hospitalized premature infants offered a rare opportunity to study the mode of transmission of this condition. In the investigation, we used serotyping, antibiotic susceptibility testing, assay of extracellular neuraminidase, and bacteriophage typing to "fingerprint" GBS strains from the two affected infants and from other colonized infants and personnel.

PATIENTS AND METHODS

On Nov 26 and 27, 1978, within a 24-hour period, two premature infants in the Michael Reese Hospital Special Care Nursery, Chicago, experienced late-onset GBS septicemia. Lethargy and apneic spells were initial symptoms in the two affected infants. They were aged 11 and 71 days and had both been hospitalized in the unit since birth. Neither infant had meningitis; both responded promptly to initial therapy with ampicillin sodium and kanamycin sulfate followed by a ten-day course of aqueous penicillin G. Blood cultures from the two infants yielded GBS serotype III.

Both infants were being cared for in open cribs in the "intermediate care" room of the nursery, along with 16 other infants. An additional ten infants were hospitalized in the adjacent "intensive care" room of the nursery.

Throat, ear, umbilical, and rectal swabs were obtained from all infants in the intermediate- and high-risk areas on Dec 7, 1978. Swabs were inoculated directly into selective broth[8] and were subcultured after overnight incubation to sheep blood agar plates. Colonies were identified as GBS by means of the Christie, Atkins, and Munch-Petersen (CAMP) reaction[9] and serotyped

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by capillary precipitation.[10] Using the same techniques, three previous culture surveys of all hospitalized neonates had been conducted in the nursery on May 18, June 26, and Oct 20, 1978. Two subsequent surveys were also carried out on Jan 9 and Feb 12, 1979.

Cultures of throat, vagina, and rectum for GBS were obtained from the mothers of all infected and colonized infants identified in the Dec 7 survey. Fifty-three of the 67 nurses and physicians working in the nursery at the time of the two late-onset cases were also surveyed for GBS carriage, including the 20 personnel who had cared for the two infected infants during the week prior to their onset of illness. Throat, vaginal, and rectal cultures were obtained from female personnel; throat and rectal swabs were obtained from male personnel.

Isolates of GBS type III were further characterized by antibiotic sensitivity patterns, neuraminidase production, and bacteriophage type. Sensitivity to erythromycin and tetracycline[11] were determined by the Kirby-Bauer technique. Extracellular neuraminidase production was assayed by the method of Milligan et al.[12] Bacteriophage typing was based on patterns of bacterial lysis by a battery of 31 streptococcal bacteriophages, as recently described by Stringer.[13]

RESULTS

The GBS type III isolates from the two infants with late-onset sepsis were sensitive to erythromycin and tetracycline, did not produce neuraminidase, and were both of phage type 7/11/12. Both sets of maternal cultures were negative for GBS, as was a set of cultures from the older of the two infants obtained in the Oct 20 survey. The identity of the two strains, the close temporal relationship of illness onsets, and the negative maternal and prior infant cultures were consistent with nosocomially acquired infection.

Culture surveys in the two areas of the nursery are summarized in the Table. In the three surveys conducted prior to the case cluster, no GBS colonization was detected in hospitalized infants. In addition to the two affected infants, the survey conducted on Dec 7, 1978, disclosed five other neonates with asymptomatic GBS colonization. Of the seven infants, throat cultures were positive in five, rectal cultures were positive in five, and ear and umbilical cultures were all negative. The five GBS isolates from asymptomatic infants were identical in serotype, erythromycin and tetracycline sensitivity, absent neuraminidase production, and bacteriophage type to those from the infected babies. The five colonized infants were of low birth weight and were located in bassinets adjacent to the two infected infants in the intermediate-care area. The group included one single birth, one of a pair of twins, and all three of a set of triplets. None was receiving "banked" breast milk feedings. Cultures from the mothers of these infants were negative for GBS, although the mother of the set of triplets had received ampicillin for postpartum fever at another hospital prior to our cultures. Subsequent culture surveys of infants hospitalized in the nursery revealed prevalences of GBS in five of 23 on Jan 9 and in one of 29 on Feb 12, 1979. The bacteriophage type 7/11/12 serotype III strain was not isolated in these surveys, although four of the five Jan 9 isolates were serotype III strains of bacteriophage type 12.

Group B Streptococcus Culture Surveys of Special-Care-Nursery Infants

	Intensive Care Area		Intermediate Care Area	
Date of Survey	No. of Infants Cultured	No. Positive for GBS*	No. of Infants Cultured	No. Positive for GBS
5/18/78	8	0	11	0
6/26/78	7	0	12	0
10/20/78	9	0	13	0
12/7/78	10	0	16	7†
1/9/79	8	1‡	15	4§
2/12/79	10	0	19	1‖

*GBS indicates group B streptococcus.
†All GBS type III tetracycline-sensitive (S) erythromycin-S neuraminidase (—); phage 7/11/12.
‡One GBS type III tetracycline-S erythromycin-S neuraminidase (+); phage 12.
§Three GBS type III tetracycline-S erythromycin-S neuraminidase (+); phage 12; one GBS type III tetracycline-S erythromycin-S neuraminidase (+); phage 27/31.
‖One GBS type Ia tetracycline-S erythromycin-S neuraminidase (—); phage not done.

The culture survey of nursery personnel conducted at the time of the two index cases revealed an overall prevalence of GBS colonization of 34%. Of the 18 colonized personnel, rectal swabs were positive in 16; vaginal swabs in 13; and throat swabs in 3. A variety of GBS serotypes were isolated (3 GBS Ia, 3 GBS Ib, 5 GBS II, and 7 GBS III). None of the seven GBS type III isolates from personnel was identical to the strain isolated from the infants with late-onset sepsis. Three of these isolates were bacteriophage type 12, one was type 11/12/27/31, and three were nontypable.

COMMENT

Our findings suggest that infant-to-infant transmission of late-onset GBS infection may occur in a special-care-nursery setting. Vertical transmission did not appear to account for the two cases observed, since both mothers had negative cultures for GBS. Transmission from nursery personnel with mucosal carriage was not documented. Although 34% of personnel were colonized with GBS, none carried the bacteriophage type 7/11/12 serotype III strain responsible for the two late-onset cases. On the other hand, all five colonized infants in the nursery were found to be carrying the identical strain. The origin of this organism and the actual means of transmission from infant to infant remain speculative. The three colonized triplets, transferred from another hospital four days prior to the onset of illness in the index cases, may have introduced the organism to the nursery. Transient carriage of GBS on the hands of personnel is the likely means of transmission between infants.

In previous studies of nosocomially acquired GBS colonization in full-term infants, 41% to 52% of those colonized were born to women with negative vaginal and/or throat cultures.[5-7] Although nursery personnel in these studies had higher rates of colonization than mothers or personnel from

other hospital areas, the investigators were cautious about interpreting this to mean that personnel carriers were an important source of nosocomial infant colonization. In fact, based on differences in serotype distribution among personnel and infants, Paredes et al[6] hypothesized that infant-to-infant cross infection was the predominant mechanism. Anthony et al,[7] using bacteriophage typing techniques, have recently demonstrated this mechanism of GBS transmission within cohorts of infants in a Los Angeles hospital, and showed that a colonized mother served as the common source for the particular strain in each cohort. In the present study, a common source was not identified, although the mother of the triplets might be incriminated. Our data rule against nursery personnel as a reservoir for the infecting strain.

Propagation from infant to infant also has been incriminated in most investigations of group A streptococcal nursery outbreaks.[14-16] Infants with subclinical omphalitis often serve as the reservoir of group A organisms, and local antimicrobial treatment of the umbilical cord, combined with systemic penicillin prophylaxis, has been required to terminate smouldering epidemics. In contrast, the GBS strain responsible for the present cases was not isolated from umbilical cultures and disappeared from the nursery without imposition of control measures. On the whole, we found asymptomatic infant GBS colonization to be relatively uncommon among the babies in this high-risk population. This may reflect frequent antibiotic use, and is similar to the findings of Sprunt et al[17] in a comparable setting.

A combined approach to "fingerprinting" of GBS strains by serotype and bacteriophage type appears to be a useful means of studying patterns of acquisition of these organisms. In our experience, antibiograms and neuraminidase production were less discriminating. Although comparable data are not as yet available in the United States, bacteriophage type 7/11/12 has been relatively rare in the United Kingdom, accounting for less than 1% of serotype III isolates.[13] The bacteriophage type 12 serotype III strain encountered among personnel and in infants during our Jan 9 survey appears to be a more common organism, and thus its epidemiologic significance remains uncertain.

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References

1. Baker CJ: Summary of the workshop on perinatal infections due to group B *Streptococcus*. *J Infect Dis* 136:137-152, 1977.

2. Stewardson-Krieger PB, Gotoff SP: Risk factors in early-onset neonatal group B streptococcal infections. *Infection* 6:50-53, 1978.

3. Ablow RC, Driscoll SG, Effmann EL, et al: A comparison of early-onset group B streptococcal neonatal infection and respiratory-distress syndrome of the newborn. *N Engl J Med* 294:65-70, 1976.

4. Steere AC, Aber RC, Warford LR: Possible nosocomial transmission of group B streptococci in a newborn nursery. *J Pediatr* 87:784-787, 1975.

5. Aber RC, Allen N, Howell JT: Nosocomial transmission of group B streptococci. *Pediatrics* 58:346-353, 1975.

6. Paredes A, Wong P, Mason EO: Nosocomial transmission of group B streptococci in a newborn nursery. *Pediatrics* 59:674-682, 1977.

7. Anthony BF, Okada DM, Hobel CJ: Epidemiology of the group B streptococcus: Maternal and nosocomial sources for infant acquisitions. *J Pediatr* 95:431-436, 1979.

8. Baker CJ, Clark DS, Barrett FF: Selective broth medium for isolation of group B streptococci. *Appl Microbiol* 26:884-885, 1973.

9. Christie R, Atkins NE, Munch-Petersen E: A note on a lytic phenomenon shown by group B streptococci. *Aust J Exp Biol Med Sci* 23:193-197, 1944.

10. Facklam RR: Streptococci, in Lennette EH, Spaulding EH, Truant JP (eds): *Manual of Clinical Microbiology*. Washington, DC, American Society for Microbiology, 1974, pp 96-108.

11. Eickoff TC, Klein JD, Daly AK, et al: Neonatal sepsis and other infections due to group B β-hemolytic streptococci. *N Engl J Med* 271:1221-1228, 1964.

12. Milligan TW, Baker CJ, Straus DC, et al: Association of elevated levels of extracellular neuraminidase with clinical isolates of type III group B streptococci. *Infect Immunol* 21:738-746, 1978.

13. Stringer J: The development of a phage-typing system for group B streptococci. *J Med Microbiol* 13:133-143, 1980.

14. Langewisch WH: An epidemic of group A, type 1 streptococcal infections in newborn infants. *Pediatrics* 18:438-447, 1956.

15. Dillon HC: Group A type 12 streptococcal infection in a newborn nursery. *Am J Dis Child* 112:177-184, 1966.

16. Nelson JD, Dillon HC, Howard JB: A prolonged nursery epidemic associated with a newly recognized type of group A streptococci. *J Pediatr* 89:792-796, 1976.

17. Sprunt K, Leidy G, Redman W: Abnormal colonization of neonates in an intensive care unit: Means of identifying neonates at risk of infection. *Pediatr Res* 12:998-1000, 1978.

Human Toxocariasis in a Rural Community

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• A questionnaire and serologic survey of a Pennsylvania community revealed that 23 (54%) of 43 study participants had antibody titers to *Toxocara canis* (enzyme-linked immunosorbent assay test [ELISA]) in the range defined as positive (≥ 1:32). Age-specific seropositivity rates were highest among adults (≥ 18 years). Positive titers ranged from 1:32 to 1:512. Seropositivity did not cluster by family, and seropositivity rates were significantly higher than those of a control group. Physical examination and laboratory tests designed to detect clinical signs of toxocariasis were performed on individuals with positive ELISA titers. Nine of 23 had a history of pica, seizures, or chronic pulmonary symptoms; however, physical examination revealed no abnormalities. Although medical examination and laboratory tests revealed a few abnormalities, neither the visceral larva migrans syndrome nor the ocular lesions characteristic of those produced by *Toxocara* sp were observed in any individual. We conclude that although certain populations may have high seropositivity rates to *Toxocara* antigens, indicating previous infection, clinical disease may be uncommon.

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The larvae of *Toxocara* sp, the common roundworms of dogs and cats, are capable of infecting human beings who ingest eggs containing infective-stage larvae.[1,2] The prevalence and distribution of human infection have remained unknown because of the nonspecific nature of the signs and symptoms and the lack of a reliable serologic test to establish the diagnosis. Recently, however, the enzyme-linked immunosorbent assay (ELISA) has been shown to give highly satisfactory results in terms of sensitivity and specificity,[3-6] and the test appears suitable for clinical and epidemiologic studies of zoonotic toxocariasis. We report the results of a clinical and serologic examination of a community with a high rate of endemic toxocariasis.

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BACKGROUND

In June 1977, the Center for Disease Control (CDC), Atlanta, was contacted by the Bureau of Children's Services, Pennsylvania State Department of Health, regarding several suspect cases of visceral larva migrans in a community. Three siblings (aged 3 to 6 years) had antibody titers to *Toxocara* sp (ELISA test) in the range defined as positive (≥ 1:32) by workers at the University of Pittsburgh, where the test was developed.[3] Lesser but measurable titers were obtained on serum specimens from the three remaining household members. In addition, five of the six members had eosinophilia. Of nine additional samples from individuals living in the same community, six demonstrated detectable antibody to *Toxocara*; therefore, an investigation was initiated.

The community is located in the Appalachian mountains of southern Pennsylvania where 70 to 100 persons live in trailers and two- and three-room houses. Most families have poorly maintained toilet facilities (privies) and obtain water from a few "springs," which are centrally located. There is no organized garbage collection, and animals, especially dogs, roam freely through the yards. The absence of paved roads or walks allows large amounts of mud, possibly containing animal excreta, to be carried indoors.

METHODS

Visits were made to all the homes and the purposes of the investigation were explained. Volunteers who consented to participate were questioned about length of residence and dog ownership and were requested to provide a blood and stool specimen. Control subjects of similar age, sex, and race were selected from a clinic population in a nearby community. In contrast to the study group, all control subjects obtained water from properly maintained wells, and had adequate toilet facilities and restricted yards. The sera were tested at CDC with use of the toxocaral ELISA test.[3,4] Stool specimens were preserved in two vials (one containing 5% formaldehyde solution and the other polyvinyl alcohol) and examined at CDC with use of direct mounts and formal-ether concentration techniques. Individuals from both study and control groups found to have positive ELISA titers were evaluated by physical examination, including ophthalmologic examination, laboratory tests (prothrombin time, hematocrit reading, WBC count and differential cell count, immunoglobulin level, and isohemagglutinin titers). Soil samples from various areas in the community were collected and examined with a formal-ether concentration. Water samples were collected from three springs in the study community and tested for total coliforms by the Pennsylvania Department of Environmental Resources.

RESULTS

Forty-three residents from 13 families comprised the study group. Of these, 23 (54%) were seropositive by the ELISA test at a titer of ≥ 1:32 (range, 1:32 to 1:512). In the control population, a positive ELISA titer (range, 1:32 to 1:128) was found in four (9%) of 44 individuals from 25 families. The seropositivity rate of the study group was significantly higher than that of the control group ($P < .001$, Fisher's exact test). Rates

Table 1.—Age-Specific Seropositivity Rates, Toxocaral ELISA Test, Bedford County, Pennsylvania, 1978*

	Study Group		Control Group	
	No.	% Seropositive†	No.	% Seropositive†
Preschool (0-5 yr)	12	33	14	7
School age (6-17 yr)	9	56	2	50
Adult (≥18 yr)	22	64	28	7
Total	**43**	. . .	**44**	. . .

*ELISA indicates enzyme-linked immunosorbent assay.
†ELISA titer ≥1:32.

Table 2.—Distribution of Positive ELISA Titers for *Toxocara* sp by Households in Study Group, Bedford County, Pennsylvania, 1978*

Household Unit	Household Members Tested, No. Positive/ No. Tested
1	4/5
2	1/4
3	2/4
4	2/3
5	1/2
6	5/6
7	1/1
8	1/1
9	1/1
10	0/2
11	0/3
12	5/8
13	0/3

*ELISA indicates enzyme-linked immunosorbent assay; ELISA titer ≥1:32.

Table 3.—Results of Clinical and Laboratory Examination of ELISA-Positive Individuals in a Community in Bedford County, Pennsylvania, 1978*

Clinical or Laboratory Examination	No. Examined	No. Abnormal (%)
History		
Pica	23	5(22)
Seizures	23	2(9)
Chronic pulmonary complaints	23	5(22)
Physical	23	0(0)
Ophthalmologic†	21	3(14)‡
Eosinophilia	19	9(47)
Anemia	19	14(74)
Prothrombin time	22	0(0)
Isohemagglutinin titers	26	0(0)
Immunoglobulin titers (IgG, IgA, IgM)	27	3(11)§

*ELISA indicates enzyme-linked immunosorbent assay.
†Funduscopic and refraction.
‡Presbyopia in two; myopia in one.
§Increased IgG levels in two; increased IgA level in one.

increased with age in the study group, but age association was not apparent among control subjects (Table 1). There were no significant differences in seropositivity rates between male and female subjects in either group. The length of residence for study group participants ranged from 3 months to 11 years. No differences were found between seropositive and seronegative participants with respect to length of residence. Seropositive persons did not cluster by family in the study group but were distributed throughout ten of the 13 participating families (Table 2). Each of the four individuals with positive titers in the control group was from a different family.

Nine (69%) of the 13 families in the study group owned dogs, and four families (31%) did not (including the two families with no persons having positive titers). In the control group, 14 (56%) of 25 families owned dogs. Three of the seropositive control individuals were from families that owned dogs. These differences were not statistically significant ($P > .05$). In both study and control groups, all families that owned dogs had obtained them as puppies.

In the study group, stool specimens were submitted by 14 persons representing six households. Parasites were demonstrated in seven specimens (*Ascaris lumbricoides* in three, *Giardia lamblia* in three, and *Chilomastix mesnili* in one). Stool specimens were submitted by 11 persons in the control group, and two of these were positive for *G lamblia*. Two of four surface soil samples collected from areas frequented by dogs were positive for *Toxocara* ova. Water samples collected from three separate sources in the involved community and tested for total coliform count were found to be grossly contaminated.

A history was taken and a physical examination was performed on 23 persons who had positive ELISA titers. Two persons reported a history of seizures (at age 3 and 10 years) in the past, and one (aged 47) had hepatomegaly associated with congestive heart failure on physical examination. Laboratory studies showed an anemia in nine of 22 individuals (age adjusted) with a mean hemoglobin level of 12.2 gm/dL and a ≥ 5% eosinophilia in nine of 22 individuals with a mean eosinophilia of 5.59%. Determinations of prothrombin time, immunoglobulin levels, and isohemagglutinin titers were also made (Table 3).

The ELISA tests were repeated after one year for a group of 23 seropositive and seronegative individuals. Only in four specimens did the titers differ from earlier results by more than two dilutions. For three of these, the titers decreased (1:128 to 1:4, 1:8 to 0, and 1:32 to 1:4), and for one the titer rose (1:2 to 1:128).

COMMENT

More than half of the persons tested in this community, both adults and children, had serologic evidence of toxocariasis; this is a much higher seroprevalence than observed in other communities. Samples of some other populations have had a toxocaral seroprevalence that varied between 0% and 13%, depending on age, geographic region, and income levels.[7] The toxocaral ELISA test has been extensively evaluated[3,6] and has been shown to be both specific and sensitive for toxocariasis. False-positive reactions caused by the presence of heterophil

antibody, C-reactive protein, or antibodies to the parasites are eliminated by previous absorption of the test serum with ascarid antigens.[3] At a diagnostic titer of 1:32, the diagnostic sensitivity was approximately 75% and the specificity was greater than 90%.[4,6] The apparent 10% nonspecificity in clinical evaluations appears to be a result of the prevalence of asymptomatic infection.

Larvae of *Toxocara* sp can invade almost any tissue of the human body. Most cases are probably subclinical, but two well-known forms of clinical expression of toxocariasis exist: one, visceral and the other, ocular.[7-9] The visceral larva migrans (VLM) syndrome occurs most frequently in children 1 to 5 years of age and is characterized by coughing or wheezing, transitory pulmonary infiltration, hepatomegaly or splenomegaly, leukocytosis, persistent eosinophilia, elevated anti-A or anti-B isohemagglutinin levels, increased immunoglobulin concentrations, and a history of pica.[7,10] Its association with pica suggests that clinical illness may be a function of the numbers of eggs ingested, frequency of reinfection, or other, as yet undefined, factors. Larval invasion of the eye is not uncommon, and the characteristic lesion is a retinal granuloma.[11,12] Ocular disease is usually seen in patients who have no other signs or symptoms of VLM, either concurrently or historically.[7-9] We were unable to find evidence of the VLM syndrome or ocular lesions characteristic of toxocaral disease at the time we performed medical examinations on seropositive persons. These negative findings support the concept derived from clinical and experimental observations that most infections caused by *Toxocara* sp are subclinical. Although some of our study population had a history of medical problems compatible with a diagnosis of VLM (seizures, pulmonary complaints, etc) these were too nonspecific to permit conclusions regarding cause.

In the past, investigators have found that children in the 0- to 4-year age range are most likely to come into contact with infective *Toxocara* eggs, and, because of a generally lower level of hygiene, are most likely to become heavily infected and manifest clinical illness. The exact mechanism of spread in this population was not determined; however, of interest is the large percentage of seropositive adults.

One possible explanation for this finding is that a positive titer does not reflect recent infection but represents persistence of antibody from an earlier infection. Thus, the seropositive adults presently living in this community could have been exposed to infection earlier in life while living in a similar environment in a different community. This would explain the lack of a statistical correlation between seropositivity and length of residence. Although this phenomenon has not been demonstrated in humans, animal studies have shown that *Toxocara* larvae may remain alive in the tissues of rhesus monkeys for ten or more years. More recently, one of us (P.M.S., unpublished data) has demonstrated that toxocaral antibody is detectable by the ELISA test at high titers in the serum of monkeys for greater than 30 months after experimental infection. Another possibility that cannot be excluded is that adults living under the conditions existing in this community may be at higher risk of infection and may have acquired infection recently.

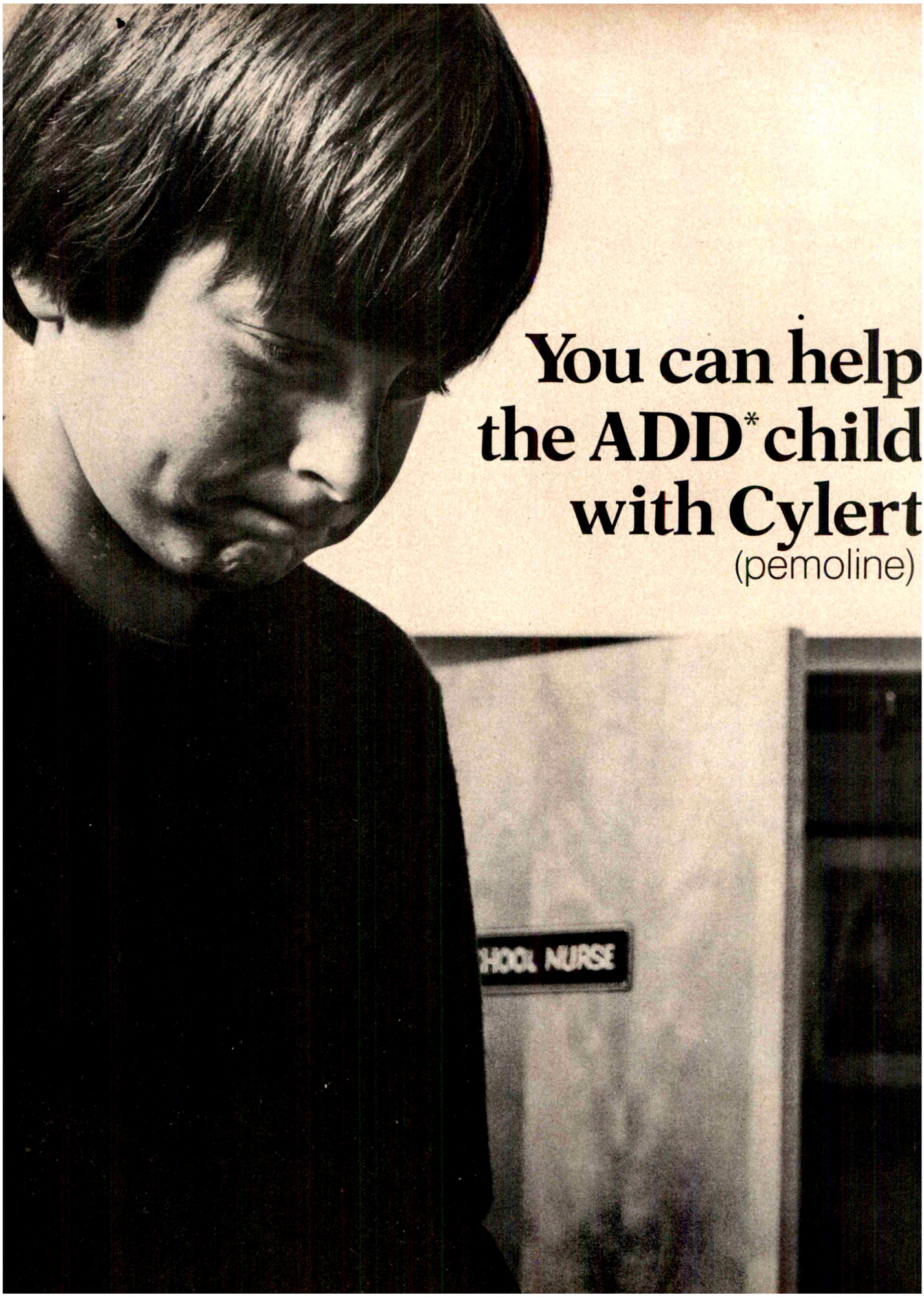
Studies on the prevalence of *T canis* in dogs in the United States revealed that 20% to 21% of adult dogs and as many as 98% of puppies may be infected.[7,13,14] If we assume this to be an accurate reflection of the nationwide prevalence of this parasite, then a combination of dogs allowed to defecate in areas of human habitation and a generally low level of personal hygiene make an ideal setting for transmission of *Toxocara* sp to humans. Indeed, the most likely source of infection in this community is the large population of dogs that roam freely through the area.

This community was not representative of the general US population, either rural or urban. Rather, it was characterized by a generally low level of hygiene and sanitation. We conclude that although clinical disease is uncommon, infection with *T canis* may be more widespread than previously indicated. A greater understanding of the epidemiologic factors and the methods required to control or prevent this zoonosis is needed.

Annette Lynch, MD, DPH, Director, Bureau of Children's Services, Pennsylvania Department of Health; Lawrence Glickman VMD, DPH, formerly at the University of Pittsburgh; Irving G. Kagan, PhD, Director, and Dorothy Allain, Parasitology Division, Bureau of Laboratories, Center for Disease Control (CDC), Atlanta; David S. Gordon, MD, Director, and Bonnie M. Jones, MT (ASCP), Immunology Division, Bureau of Laboratories, CDC: the public health nurses at Bedford and Somerset Counties, Pennsylvania, under the supervision of Karen Chirillo, RN; and Maurice D. Geiger, DDS, MPH, District Executive Director, South Central District, Pennsylvania Department of Health, all assisted in this investigation.

References

1. Beaver PC, Snyder CH, Carrera GM, et al: Chronic eosinophilia due to visceral larva migrans. *Pediatrics* 9:7-19, 1952.
2. Beaver PC: Toxocarosis (visceral larva migrans) in relation to tropical eosinophilia. *Bull Soc Pathol Exot* 55:555-562, 1962.
3. Cypess RH, Karol MH, Zidian JL, et al: Larva-specific antibodies in patients with visceral larva migrans. *J Infect Dis* 135:633-640, 1977.
4. Glickman LT, Schantz PM, Dombroske RL, et al: Evaluation of serodiagnostic tests for visceral larva migrans. *Am J Trop Med Hyg* 27:492-498, 1978.
5. Schantz PM, Meyer D, Glickman LT: Clinical, serologic, and epidemiologic characteristics of ocular toxocariasis. *Am J Trop Med Hyg* 28:24-28, 1979.
6. Pollard ZF, Jarrett WH, Hagler WS, et al: ELISA for diagnosis of ocular toxocariasis. *Ophthalmology* 36:743-749, 1979.
7. Glickman LT, Schantz PM, Cypess RH: Canine and human toxocariasis: Review of transmission, pathogenesis, and clinical disease. *J Am Vet Med Assoc* 175:1265-1269, 1979.
8. Schantz PM, Glickman LT: Toxocaral visceral larva migrans. *N Engl J Med* 298:436-439, 1978.
9. Zinkham WH: Visceral larva migrans: A review and reassessment indicating two forms of clinical expression—visceral and ocular. *Am J Dis Child* 132:627-633, 1978.
10. Mok CH: Visceral larva migrans—a discussion based on a review of the literature. *Clin Pediatr* 7:565-573, 1968.
11. Brown DH: Ocular *Toxocara canis:* II. Clinical review. *J Pediatr Ophthalmol* 7:182-191, 1970.
12. Welch RB: Intraocular *Toxocara*, in Ray SJ, Smith RE (eds): *Selected Topics on the Eye in Systemic Diseases.* New York, Grune & Stratton Inc, 1974, pp 177-193.
13. Heiner DC, Kevy SV: Visceral larva migrans. *N Engl J Med* 254:629-631, 1956.
14. Scothorn MW, Koutz FR, Groves HF: Prenatal *Toxocara canis* infection in pups. *J Am Vet Med Assoc* 146:45-49, 1965.



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*ADD: Attention Deficit Disorder (formerly called MBD, Minimal Brain Dysfunction), or the Hyperkinetic Syndrome. Please see next page for Brief Summary.

ABBOTT

9083319

Cylert® (pemoline)

DESCRIPTION: CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one.

Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg./ml.) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg./ml.

CYLERT (pemoline) is supplied as tablets for oral administration.

CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities; nystagmus and nystagmoid eye movements; and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Abbott, Pharmaceuticals, Inc.
North Chicago, IL60064, U.S.A.

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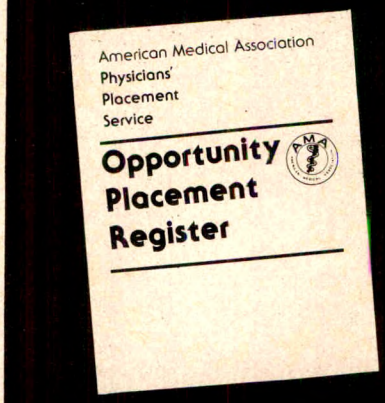

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Review

Food Sensitivity

A Critical Review and Practical Approach

S. Allan Bock, MD

One of the most common problems brought to the attention of today's pediatrician is the question of a possible association between ingestion of a particular food and symptoms experienced by a child. Publications to which parents have ready access, including newspapers, are replete with reports of various adverse reactions to foods in children (commonly called "allergy"). Because the pediatrician is considered by parents to be an authority on health matters, he is often requested to comment on reports that parents have read. This is a difficult task because often the reports are based on comments made at meetings that are not available in print for the pediatrician to analyze critically. Even if there is a written report, it may be difficult for the pediatrician to spend the time required to help parents become critical readers of lay publications.

This review considers the topic of food sensitivity, including the basic principles and the clinical approach. A step-by-step procedure is outlined in a later section for those physicians who desire to take the time to evaluate their own patients for food sensitivity. Details not included in this review may be found in articles in specialty publications.[1,2] It is hoped that a critical evaluation of this subject will aid pediatricians in their daily interaction with patients who are concerned with this subject.

From the National Jewish Hospital and Research Center, and the University of Colorado Health Sciences Center, Denver.

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The term "food sensitivity" has been adopted and the term "food allergy" abandoned because the latter has been misused by application to a multitude of anecdotally reported syndromes that have not been shown to be associated with immunologic interactions. This review will be primarily limited to a discussion of those reactions that do have associated immunologic laboratory findings. However, because pediatricians are so commonly queried about other syndromes, comments will be offered about these conditions at the end of this review.

IMMUNOLOGIC PRINCIPLES

Antigen Sensitization

Though this review is not meant to be an exhaustive discussion of immunology, certain fundamentals need to be considered in order to understand the practical approach developed in a later section. When antigen is ingested, initially it must be processed and presented to immunologically competent cells so that sensitization may occur or a reaction appear in a sensitized person. Antigen reaches immunocompetent cells via the mucosa (either respiratory or gastrointestinal [GI], which have a common embryologic origin), through the skin, or perhaps by crossing the placenta in the fetus. Very little is known in humans concerning which molecular antigens can cross the placenta; however, it is well known that the fetus produces immunoglobulins. Premature infants have been shown to produce antibodies to bovine serum albumin.[3] The form in which most food proteins cross the mucosal barrier is also incompletely understood, but it is obvious that antigenic determinants of proteins and perhaps relatively intact proteins themselves do cross the mucosa, with the result that all infants with a normal immune system make antibodies to foods in their diet, especially to milk[4,5] (and from written communication of C. D. May, MD, S. J. Fomon, MD, and L. Remigio, 1980).

Antigens (both food and microbial) first encounter the immune system at the mucosal surface and in the lumen. These reactions have not been well elucidated in humans for food antigens, but there are animal models that suggest an investigative approach to be pursued in humans.[6,7]

When food antigens cross the GI mucosa, they first encounter immunologically reactive cells in the lamina propria. Most of these are plasma cells of which the largest number are producing IgA. It has been shown in humans that sensitized mast cells may also be encountered in the intestine, and if activated they will degranulate.[8] Antigens gain access to Peyer's patches through "specialized M cells."[9] The stimulation of Peyer's patch lymphocytes and the resulting circulation of these cells through the lymphatic system with subsequent homing of the lymphocytes to the lamina propria is an area of active investigation, which when unraveled should aid our understanding of immunologic events in the intestine. Proteins or fragments thereof reach the circulation with enough antigenicity to stimulate clinically apparent reactions at sites distant from the point of absorption.

Antigen-Antibody Interaction

When antigen encounters sensitized cells, a sequence of immunologic reactions occurs that must be carried to completion for clinical symptoms to be manifested (Fig 1). The presence of specific antibodies (sensitization) is not synonymous with symptoms, and the difference will be discussed in detail in a subsequent section. Antigen-antibody interaction can lead to lymphocyte proliferation, direct cytotoxicity, or release of numerous mediators. These cells or their mediators then interact with end organs; this may then result in clinically observable symptoms.

Each step in this sequence is governed by a stimulus-response relationship that must

be satisfied before the next step may occur (Fig 2). If the relationship is not satisfied at each step, ie, if a certain threshold for reaction is not exceeded, then the next step will not occur and no clinically apparent symptoms will be observed. Thus, it should not be surprising to learn that a child has antibodies to one or more proteins yet exposure by the usual routes does not result in symptoms.

CLINICAL PRINCIPLES

Definition of Terms

One of the most troublesome aspects of the subject of food sensitivity is misuse of the term "allergy." This term will not be used here; instead, the term food sensitivity will be used to avoid some of the confusion. The dilemma has arisen because the term allergy has two components, namely, sensitization (the presence of antibodies) and the presence of symptoms. These are easily confused for one another when the considerations discussed earlier are forgotten. When patients describe reactions to foods and suggest that they are due to allergy, the patients should be encouraged to use the term adverse reaction to food until the symptoms have been objectively confirmed and the mechanism has been identified.

The terms "symptomatic sensitivity" and "asymptomatic sensitivity" are much more useful than the term food allergy when considering immunologically mediated adverse reactions to food. Symptomatic sensitivity indicates that sensitization has been demonstrated, the adverse reaction has been objectively confirmed, and other causes of reaction have been eliminated. Asymptomatic sensitivity means that sensitization has been demonstrated, but the patient is able to tolerate the food when it is consumed as part of the diet in usual portions prepared by customary means.

Differential Diagnosis

It is not the purpose of this review to discuss in detail the differential diagnosis of adverse reactions to foods; however, it must be remembered that immunologic reactions are not the only cause. Enzyme deficiencies, particularly lactose deficiency, are well known to all pediatricians. Less common enzyme deficiencies such as galactosemia will need to be considered in infants as possible causes of adverse reactions to foods. Toxins in foods (eg, aflatoxins), while not common, may be an occasional cause of symptoms and must be considered. There are both natural toxins and contaminants that may be products of modern living.[10] Examples of natural constituents are alkaloids, as found in mushrooms; hemagglutinins, as found in beans; goitrogens, as found in cabbage; cyanide, as found in the stones of fruits; pressor amines, as found in bananas; and oxalates, as found in rhubarb. Examples of contaminants are saxitoxins, ergot, aflatoxins, penicillin, mercury, and pesticides. Additives, such as dyes and nitrites, must also be considered.

In addition, there may be as yet unidentified biochemical reactions in the intestine or elsewhere in the body that are initiated by ingested substances but have no immunological reactions associated with them. The confirmation of this conjecture must await further investigation.

Beliefs about reactions to foods greatly influence the outcome of food challenges. As will be shown later, many reactions to foods, which are plausibly described by reasonable parents, simply cannot be confirmed objectively. The final category of adverse reactions to foods are immunological reactions, and the remainder of this review will be devoted to the interaction of foods and components of the immune system.

MANIFESTATIONS OF FOOD SENSITIVITY REACTIONS

Reaginic Reactions

Most reviews of foods sensitivity divide the reactions into various syndromes or constellations of symptoms. It would seem more helpful to attempt to divide these reactions by the mechanism that can be shown to be associated or is under investigation. Therefore, the following scheme has

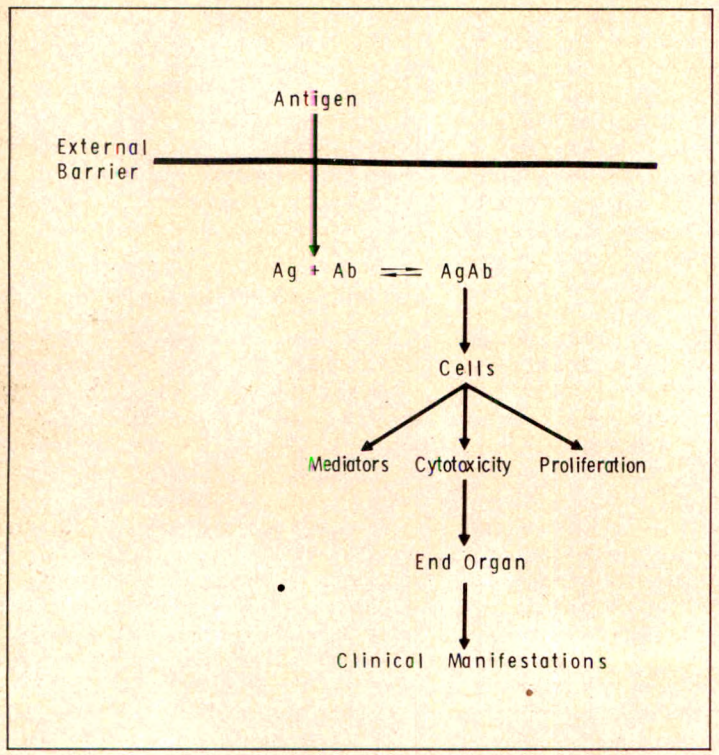


Fig 1.—Immunologic events after exposure of a sensitized person to antigen.

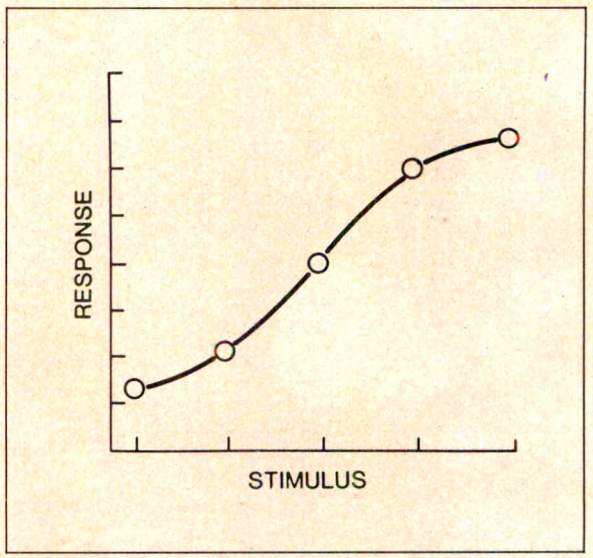


Fig 2.—Relationship between stimulus and response.

been devised to take into account the current state of the knowledge of immunological adverse reactions to foods, and confirmed manifestations have been divided as follows: reaginic reactions include anaphylaxis, abdominal pain, vomiting, diarrhea, angioedema, rash, urticaria, rhinitis, and asthma. Nonreaginic reactions include enteropathies such as vomiting, diarrhea, occult bleeding, protein-losing, and malabsorption; urticaria; allergic dermatitis; pneumonitis; and hemosiderosis.

Reaginic reactions are those that can be shown to have specific, identifiable IgE[11,12] or IgG reagin[13,14] associated with the clinical symptoms provoked by the particular food. These manifestations are almost exclusively limited to the GI tract, the skin, and the respiratory tract. Behavioral aberrations that have been noted in recent studies[15] have accompanied the discomfort created by the reaction occurring in another system. Older children who become irritable or have a mood change are able to report specific discomfort. Behavioral manifestations as the *sole* symptom of adverse reactions have not been objectively confirmed in studies at the National Jewish Hospital, Denver. Anaphylaxis to foods includes systemic manifestations; fortunately, it is quite uncommon in children.

Nonreaginic Reactions

Gluten-Sensitive Enteropathy.—Nonreaginic reactions to foods have been less clearly demonstrated, both clinically and immunologically, than reaginic reactions. Gluten-sensitive enteropathy (celiac disease) is the adverse reaction to food for which there is currently the most data supporting a nonreaginic immunologic mechanism as the etiology of the illness. Elegant in vitro[16] organ culture studies have shown that the villous architecture becomes flattened by the addition of gluten to the intestine-containing culture medium, but in addition to the gluten there is an endogenous effector that must be present or the histologic alteration will not occur. It is hypothesized that this effector is immunoglobulin. It has also been shown that the intestine of a gluten-sensitive patient produces increased amounts of specific antigluten antibody in response to challenge with gluten. This subject has been reviewed in detail elsewhere, and the interested person should read the details of these very informative investigations.[17-19]

In addition to the immunologic data, genetic investigations have shown a link between gluten-sensitive enteropathy and the histocompatibility antigen HLA-B8.[16,20] There is also a study showing an association between the disease and HLA-Dw3.[21]

Acute Gastroenteropathy.—Reactions consisting of vomiting and diarrhea with onset usually within 12 to 48 hours after ingestion of the offending food have been variously termed intolerance, allergy, idiosyncrasy, and intractable diarrhea. The two most common offending foods in this group are cow's milk and soybean derivatives. The best term for this type of reaction is acute gastroenteropathy.

Symptoms begin within a few weeks or months of the introduction of artificial formulas into the infant's diet. The problem is transient, so that between the ages of 2 and 3 years the child can tolerate the offending substance. If the responsible food is not identified and removed from the diet, the diarrhea may become intractable and sometimes fatal.[22,23]

The interval of hours to days between ingestion of the causative food and appearance of symptoms may be due to the time required for the pathologic process to become marked enough to produce symptoms. This is not properly referred to as a delayed reaction in an immunologic sense because the interaction of antigen and antibody or antigen and sensitized cells may occur within minutes of ingestion, though symptoms do not appear until the reaction has progressed to a point as yet undefined.

Examination of the mucosa of the jejunum in these children often reveals a characteristic flattening of the villi and infiltration of the lamina propria with lymphocytes, plasma cells, and eosinophils.[24-26] Because the lesion in the small bowel is a patchy lesion (unlike that in gluten-sensitive enteropathy), it may be missed when only a single biopsy is performed. Furthermore, the question of exactly when to perform the biopsy in relation to challenge with the offending food and production of symptoms is currently under investigation. An excellent, recent study has suggested that definitive information may be obtained by serial biopsies associated with challenge.[27] These children ordinarily do not exhibit evidence of reaginic sensitization nor do they have symptoms characteristic of reagin-mediated sensitivity.

Although soybean was mentioned above as a cause of acute gastroenteropathy, to my knowledge there is currently only one report in the literature of a biopsy showing the characteristic alteration of the mucosa after ingestion of soy.[28] In fact, the number of well-documented cases of adverse reaction to soy is, in my search of the literature, quite small considering the number of children ingesting soybean-derived formulas.[15,29-31] Thus, it would seem premature to become alarmed about the substitution of soybean products in place of cow's milk formulas in the vast majority of infants in whom this feeding is used.[32] This is especially true in view of the fact that infants produce circulating antibodies to proteins they consume without becoming symptomatic.[3-5]

Chronic Gastroenteropathy.—Within the last two decades there have been descriptions of infants and a few children suffering from several chronic symptoms: iron-unresponsive hypochromic anemia, edema, hypoproteinemia, and failure-to-thrive that is associated with occult blood and protein loss from the intestine.[33-35] It was found that removal of whole cow's milk from the diet allowed resolution of the symptoms, and subsequently these children were able to tolerate milk without apparent recurrence of their symptoms. Thus the condition, while chronic at an early age, seems to be transient with respect to future maturation as opposed to gluten-sensitive enteropathy, which is permanent.

A few of these patients[33] had episodes of urticaria, eczema, asthma, or rhinitis, suggesting involvement of a reaginic reaction. Unfortunately, the presence of reaginic antibodies was

not systematically sought; however, many of the patients were found to have elevated levels of circulatory precipitins to cow's milk proteins.[34,35]

Only a few of these patients have had small-bowel biopsies that revealed eosinophilic infiltration of the lamina propria, but the villi were normal or only slightly altered.[33]

More recently, Katz et al[36] have described a group of children with diarrhea, eosinophilia, and failure-to-thrive in whom biopsy of the gastric mucosa more regularly revealed infiltration with eosinophils than did biopsy specimens of the jejunum. This constellation of findings has been termed eosinophilic gastroenteritis. These children have not uniformly been found to have an identifiable offending food in the diet.

Chronic Pneumonitis.—In 1962, Heiner et al[37] described a group of infants in whom there was an association between high titers of precipitins to cow's milk proteins in the serum and a chronic pneumonitis. Subsequently, only a few other similar children have been described.[38-41] The infants' symptoms included vomiting, choking, coughing, and dysphagia, whereas diarrhea was unusual. Laboratory studies usually revealed hypochromic anemia and eosinophilia, and pulmonary infiltrates were found when chest roentgenograms were examined. In some cases, these infiltrates were found to be due to pulmonary hemosiderosis, and while hemoptysis was not usually manifested clinically in infants, examination of gastric contents showed the presence of macrophages containing iron. Removal of cow's milk from the diet resulted in resolution of the symptoms of these patients. The mechanism whereby these lesions were produced is currently unclear. It may be that a combination of nonreaginic and reaginic mechanisms are involved. Pediatricians should maintain an awareness of this constellation of symptoms so that other cases may be properly identified and the mechanism sought.

Current Knowledge of Immune Mechanisms in Nonreaginic Reactions.—It should be quite clear to the reader that the foregoing discussion constitutes a current attempt to classify certain syndromes by associated immunologic mechanisms. Ultimately, some of the immunologic reactions may be found to be etiologic. As we learn more about these conditions, this classification will become refined and more specific. The hiatuses in our knowledge serve as a challenge to continue to pursue the mechanisms of these illnesses.

Ultimately, the classification will probably be more complicated than presented here; however, there will eventually be more precise diagnostic tools to aid in the categorization of the individual patient. The pediatrician should concentrate on arranging an orderly diagnostic approach to each patient, based on current comprehension of etiologic mechanisms of adverse reactions to foods, both immunologic and nonimmunologic. (See next sections for practical procedures.)

DIAGNOSTIC PROCEDURES

Some people have adopted the attitude that if a food seems to be causing a reaction it should be removed from the diet and nothing further need to be done. This approach may be viewed as impressionistic empiricism and it leads to faulty diagnosis and nutritionally inadequate diets in some patients, especially young children. The proper approach expected of practitioners of scientific medicine requires more effort and thought. The practical solution is to ascertain the correct diagnosis by proper testing and then to prescribe the treatment based on this diagnosis. The next sections discuss an orderly approach to the problem, using currently available techniques; it is hoped that some of the myths surrounding the subject of diagnosis of food sensitivity will be dispelled.

Double-blind Food Challenge

The most important procedure in the study of adverse reactions to foods is the *objective, unbiased confirmation or refutation* of the history. This is accomplished by arranging that the food under suspicion be administered in such a fashion that neither the child nor the observers are aware of which food is being consumed. In children less than 5 or 6 years of age, blind challenge is performed by hiding the challenge food in some tolerated food. If the challenge food is a liquid, it can often be mixed with milk or formula that the child regularly consumes. Solid or semisolid foods can usually be hidden in applesauce. This procedure is often facilitated by use of a blender, which converts the mixture into a puree. The red applesauce created by blending strawberries in applesauce is well tolerated by young children who seem not to care about the color. In order that the mother and/or other observers remain unaware of the nature of the contents of the challenge, they may be asked to leave the room while the challenge is administered.

For children about 5 years or older, foods can be placed in capsules after having been crushed or dried. Many foods commonly incriminated as causes of adverse reactions are readily available in a dry, powdered form, eg, milk, egg white, and cereal grains (flour); peanuts can be easily crushed. Foods with a large liquid content need to be lyophilized before encapsulation, which does require the cooperation of someone with a freeze-drying apparatus. However, large quantities of foods may be infrequently prepared, and their shelf life seems to be in excess of a year, even at room temperature.

The procedure for double-blind challenge is as follows: eliminate the suspected food from the diet for at least one week; provide a diet of foods rarely causing reactions; introduce the challenge food in opaque capsules or hidden in nonoffending foods; arrange to have the subject and the observers blind; administer the challenge food in increasing amounts; and record manifestations systematically. Hospitalization may occasionally be required when the history strongly suggests a period of one or more days between the ingestion of the food and the onset of symptoms. If the child is taking medication for a chronic illness, it is essential that the medication regimen be stabilized and that the patient be as symptom-free as possible. Antihistamines should not be administered during challenges. The capsules are given in increasing doses,

with the initial dose, the size of the increments, and the length of time between doses being determined by the patient's history and by easily acquired experience. When a single dose of about 8 g has been tolerated blindly, the food is then given openly in usual portions prepared by customary means to be sure that the food will be tolerated. The latter procedure of giving the food openly ensures that considerations such as the effects of cooking or digestion are eliminated by the food being tolerated when eaten in usual portions prepared by customary means.

Placebo challenge is often not necessary, especially if more than one food is under suspicion so that the patient does not know what is in each challenge. When equivocal results are obtained, challenge with capsules containing dextrose as placebo is undertaken.

The importance of objective confirmation of even the most impressive history (except for anaphylaxis) cannot be stressed enough. A later section will show the results of food challenges. Children with histories of anaphylaxis to a food are *never* challenged with that food.

Skin Testing With Extracts of Foods

Textbooks on allergy almost invariably contain the statement that skin testing for foods is worthless or that these skin tests result in too many "false-positive or false-negative reactions." When the basis for these statements is sought in the scientific literature, it is not, to my knowledge, found. The idea that skin tests in which extracts of foods are used are not helpful is one of the major myths about allergy and is difficult to dispel. Just how these ideas have arisen is unclear, but it is the purpose of this section to refute these claims.

Extracts of foods (or inhalants) are like any other reagent used in a laboratory in that their efficacy cannot be automatically assumed. These extracts must be verified, which entails showing that they do not cause nonspecific or irritant reactions in anyone and that they do detect the presence of specific antibody. Using a group of eight food extracts to test 54 nonatopic individuals aged 2 to 60 years, it has been shown that these extracts do not produce nonspecific irritation. In addition, using extracts of 20 foods to perform a skin test on highly atopic children, it was shown that all children did not react to all extracts of foods, thus again refuting the idea of extracts of foods as irritants.[11]

Proof that extracts detect specific antibody ideally requires two pieces of evidence: correlation of the positive skin-test result with a positive double-blind food challenge; and another laboratory test to confirm the skin-test result. In studies performed at the National Jewish Hospital, both of these factors have been used in confirming the usefulness of skin testing.[11,12]

Having learned that extracts of foods used in skin testing are not nonspecific irritants and that they do detect specific antibody, it then becomes important to determine if they are helpful diagnostically. There are three major techniques whereby skin tests are applied to patients: (1) puncture test; (2) scratch test; and (3) intradermal tests. The puncture test is performed by applying drops of extract, usually of 1:20 or 1:10 weight/volume (W/V) concentration, to the back or arms. A small needle is then passed through the drop and into the skin far enough to create a small indentation but not far enough to draw blood. Scratch tests are performed by making a series of 5-mm scratches on the patient's back with a 26- or 27-gauge needle. Drops of extract of the same concentration as used for the puncture test are then placed over the scratches. Intradermal skin tests are performed by injecting intradermally the smallest amount of a 1:1,000 to 1:100 W/V concentration of extract that raises a visible bleb (usually about 0.02 cu cm). Controls performed simultaneously include a skin test with the diluent to determine nonspecific skin reactivity and a control with histamine to determine the reactivity of the patient's skin to that mediator. These controls are applied by the same technique as that used for the extracts.

Results are determined 15 to 20 minutes after application by measuring the size of the wheal and the erythema. There are many systems in current vogue for measuring skin tests. Measurement of the mean diameter of the wheal produced by the extract minus that of the diluent control yields the most helpful information. In the studies performed at the National Jewish Hospital cited in this review, a definitely positive skin-test response by the puncture technique is a wheal that is 3 mm or greater in diameter, after any bleb due to a reaction to the diluent control is subtracted (ie, a net wheal $\geq$3 mm).

The pediatrician should request of the allergist to whom he refers patients specific information regarding concentration of extracts, technique used, and interpretation of the results. The most important aspect of skin testing is proper interpretation of the results. As discussed in an earlier section, the presence of sensitization (as detected by a definite skin-test response) does not automatically predict the existence of clinical symptoms. There are a number of ways in which allergists determine whether or not skin-test responses are notable.

Determination of the clinical importance of skin-test results relies on three types of information: (1) the history may be so strongly correlated with the results of skin testing that there is no doubt about the association; (2) a challenge may be performed (blind food challenge, bronchial provocation test, or nasal provocation test as appropriate) to confirm the results of skin testing; and (3) extrapolation from the results of correlation studies may be used to predict the probability of a reaction occurring. For food sensitivity, the use of the double-blind food challenge is mandatory; selection of subjects for this procedure is discussed below.

Radioallergosorbent Test (RAST)

The RAST is a radioimmunoassay that has been used extensively by allergists to measure circulating levels of IgE antibody to specific antigens. Briefly, the test works as follows. An antigen is bound to a solid phase support (often paper disks), patient serum thought to contain IgE antibody specific for the antigen is added,

then a radiolabeled anti-IgE is added and after proper incubation and washing at each step the mixture can be counted in a gamma-radiation detector and the quantity of antigen-specific IgE can be determined.

There has been some controversy about the use of this test amongst allergists, especially for use in food sensitivity. It has been said to be superior to skin testing because it is "less dangerous" and "more reliable." As discussed above, skin testing, properly performed and interpreted, is reliable and clearly not dangerous. Recent literature has shown,[42] and many workers in the field agree, that the RAST is no more sensitive or reliable than skin testing, although that conclusion is not always clearly stated in journal articles. Problems with the RAST are that it detects circulating IgE, not cell-bound IgE, the latter being the portion responsible for mediator release; it is expensive; it requires use of radiation and attendant precautions; the results are not immediately available; circulating IgG antibody may interfere with the test; and the RAST, like the skin test, is only semiquantitative as performed in the majority of commercial laboratories. The test is very useful for research purposes and for standardization of allergenic extracts. At present, it is our opinion that the general use of the RAST for allergy testing is not appropriate; the test should be limited to research applications by persons who understand the limitations of the information provided.

Determination of Circulating Nonreaginic Antibodies to Food Protein

Investigators in the past have examined circulating levels of antibodies to cow's milk proteins.[3,43] These studies have measured the quantity of circulating antibody but have usually analyzed the data collected in terms of prevalence or incidence of detectable antibody rather than in terms of quantity. It has become well known that children with a normal immune system who drink cow's milk will make antibodies to some of the proteins[4,5,44,45] (and aforementioned communication of May et al).

More recently, children with various symptoms have been examined to see if the quantity of antibody to food proteins in the circulating blood provides any useful information. Differences have been found between levels of antibodies to milk protein in young children (<3 years of age) who have adverse reactions to cow's milk (both reaginic and nonreaginic) but who have consumed enough milk so that substantial quantities of antibody have been produced. In addition, older children have been found to have elevated levels of circulating antibodies to cow's milk protein (considerably above age-matched controls) when they have symptomatic food sensitivity to another food (eg, peanuts) but can drink milk with apparent impunity.[4,5]

This test is not widely available at present; however, further research, especially in children less than 3 years of age, may show it to be a test that would provide diagnostic assistance. Space does not allow a full explanation of the technique. It is a type of radioimmunoassay that could easily be performed in the diagnostic laboratory of a reasonably sized hospital.

GI Biopsy

Examination of biopsy specimens of the jejunum has long been the definitive method for making a diagnosis of gluten-sensitive enteropathy (celiac disease). It remains the only way at present to clearly confirm the diagnosis when accompanied by withdrawal and challenge with gluten. Biopsy studies are also the only current means by which to study the mechanism of gluten-sensitive enteropathy.

As mentioned earlier the histopathology of cow's milk protein-sensitive enteropathy, and the reported case of soy protein-sensitive enteropathy proven by biopsy results, are substantially the same as that seen in gluten-sensitive enteropathy. Gluten-sensitive enteropathy is a diffuse process involving the entire small bowel down to whatever level it has progressed. Cow's milk protein-sensitive enteropathy by contrast is a patchy lesion, and thus the altered mucosa may be missed by a single biopsy. Furthermore, the biopsy does not provide information about the degree of involvement. Despite these limitations, study of biopsy specimens of the small bowel will remain a very useful and important technique until better diagnostic tests are developed.

Katz et al[36] have shown that biopsy of the gastric mucosa may be useful in determining eosinophilic gastroenteritis when the small-bowel biopsy results are normal. The stomach is obviously easier to perform biopsy on than is the small bowel, and when eosinophilic gastroenteritis is suspected, a gastric mucosal biopsy is appropriate.

In children with a colitis syndrome secondary to cow's milk protein, results of rectal biopsies have been shown by Gryboski[46] to be useful. At present there is, to my knowledge, no good evidence that rectal biopsy is helpful diagnostically when the injury is in the small intestine. However, since rectal biopsy is much easier to perform, further investigation in this area seems warranted.

Other Diagnostic Procedures

Three other areas of immunology have been investigated in a preliminary manner with regard to their possible relationship to food sensitivity: alterations of complement, immune-complex formation, and cell-mediated immunity.

Changes in complement levels have been measured during cow's milk challenge, but the data conflict with one study that shows a change and another that does not confirm this result.[24,47] Another study reported preliminary evidence of an alteration in the alternative complement pathway while subjects were drinking cow's milk.[48] One baby had complement levels that were altered during a symptomatic sensitivity reaction to rice, which was also associated with the presence of reagin.[49]

The presence of circulating combinations of food antigen and antibody to food (immune complexes) has just begun to be looked for in patients with suspected food sensitivity. Some claims have been made about the possible association between immune complexes from milk protein and nephrotic syndrome, but these have

not been, to my knowledge, rigorously confirmed by use of the scientific method.[50] In an effort to explain the mechanism of these reactions, recent studies have begun to look for antibody and antigen in the tissue of patients who react to gluten[17,18] and to milk.[51]

To my knowledge, at present the association of cellular immune processes and food-sensitivity reactions has been inadequately examined, and the data for patients with gluten-sensitive enteropathy is inconclusive.[52] May and Alberto[53] have shown that lymphocytes from normal children and children with food sensitivity can be stimulated to the same degree by food proteins.

It seems clear that these three areas are in need of systematic, scientific investigation in order to determine if they play a role in immunological reactions to foods.

A PRACTICAL APPROACH TO PATIENTS COMPLAINING OF ADVERSE REACTIONS TO FOODS

History and Differential Diagnosis

As in most areas of pediatric practice, the most important part of an evaluation for a patient complaining of an adverse reaction to a food is the history. The following facts should be obtained for every child: (1) a free-flowing description of the symptoms and course of the reaction; (2) time between ingestion of the food and onset of symptoms; (3) when the reaction last occurred; (4) how many times the food has caused a reaction; (5) what quantity of food is required to evoke the reported reaction; and (6) what is the character of any stools, nasal discharge, sputum, etc.

When the history has been obtained, the physician is usually faced with a list of manifestations as discussed earlier. It is then necessary to consider the differential diagnosis and determine which category is most likely to explain the described symptoms.

Children 3 Years of Age or Older

Present knowledge allows division by age of the diagnostic approach for children into two groups when a food sensitivity reaction is suspected. In children 3 years of age or older, skin tests with extracts of foods are performed as previously described. When the puncture skin test with a 1:20 W/V concentration of extract gives a definitely positive result, the child undergoes a double-blind food challenge. If the puncture test is negative, the food is placed openly in the diet and the child is observed for a reaction.

The cases of 132 children 3 years of age or older with an impressive history of an adverse reaction to a food were evaluated in this manner. The adverse reaction was confirmed in only 42% of the children (22% of the double-blind food challenges). There were 26 reactions to peanuts (a legume); 15 to other nuts; 11 to egg; six to milk; two each to soy and shrimp; and one each to banana, tuna, chicken, and trout. In these older children, the puncture test was definitely positive for each food for which the double-blind challenge was confirmed, and all reactions occurred within two hours of the challenge. Reactions were caused by 20 to 8,000 mg of dried food. Gastrointestinal manifestations were evoked most commonly, skin reactions were next, and respiratory reactions were least common. Alterations in behavior accompanied some of the above reactions but did *not* occur as *sole* manifestations and were all related to discomfort experienced from the primary reaction. No child had anaphylaxis or a reaction requiring any more than minor treatment with diphenhydramine hydrochloride.

In the 58% of children whose history of food sensitivity was not confirmed, the food was tolerated when reintroduced into the diet in usual portions prepared by customary means. It is not possible to easily explain how these children each came to have an impressive history of adverse reaction except to say that many symptoms were spuriously associated with ingestion of various foods. It will be noted that none of the confirmed reactions were to chocolate, strawberry, or tomato. There are probably children who do react to these foods, but the number of these reactions is certainly much less than is commonly believed.

It should be emphasized that in this age group, in this study, all children who had an objectively confirmed symptomatic sensitivity to a food were identified by the puncture skin test using a 1:20 W/V concentration of verified extracts. Verification of these extracts, as previously described, has been found to be of utmost importance.

Children Less Than 3 Years of Age

In children less than 3 years of age, it is of primary importance to objectively confirm the existence of the adverse reaction. Research is continuing in an effort to determine which diagnostic tests might be helpful in this age group. Skin testing is quite useful even in young children if it is properly performed and interpreted. The cases of 71 children who were less than 3 years of age and who had impressive histories of adverse reactions to foods were evaluated. Symptoms were evoked in 26 (37%) of the children and in 38 of 120 (32%) double-blind food challenges. Of the 38 reactions, 13 were to milk; seven were to soy; four were to peanut; and one each was to fish, wheat, and squash.

The 26 children who reacted may be divided into two groups. Twenty subjects experienced symptoms within two hours of the food challenge, and in these the puncture skin test, performed as described, were positive for 26 of 30 positive food challenges. This illustrates that the puncture test is useful even in these young children. These children would be classified as having had reagin-mediated symptomatic sensitivity.

Six children had the onset of symptoms more than four hours after the double-blind food challenge. The puncture test was definitely positive for only one of the eight reactions to food and this result may not have been related to the mechanism that caused the reaction. The manifestations in these children all involved the GI tract or the skin. They would be classified as having had nonreagin-mediated symptomatic sensitivity.

When the child's problem is chronic diarrhea that is thought to be precipitated by food ingestion, an attempt

should be made to associate the onset and perpetuation with one or more foods so that a specific diagnosis can be formulated. Whenever appropriate, a small-bowel biopsy should be performed.

At present, circulating antibodies to foods are being determined in serum from these children at the National Jewish Hospital because the results aid in determining which cases to evaluate most vigorously. Perhaps this test will be more widely available in the future.

Recapitulation of Practical Approach

The following is a brief statement of the current practical steps used at the National Jewish Hospital for evaluation of the cases of children with a history of adverse reaction to a food. First, the history and physical examination are completed, the differential diagnosis is considered, and appropriate laboratory tests are undertaken to eliminate nonimmunologic mechanisms. If the child is over 3 years of age and has an impressive history of reaction, a puncture skin test is performed. If the puncture skin test is positive, a double-blind food challenge is then performed. If the double-blind food challenge is positive, the food is then eliminated from the diet. If the double-blind food challenge is negative, the food is then reintroduced openly into the diet and the child is observed to be sure that no reaction is occurring.

If the puncture skin test is negative, then the food is reintroduced openly into the diet and double-blind challenge is not performed unless there is some untoward reaction that is observed when the food is eaten openly. It should be emphasized that it is not always necessary to use a placebo for the elimination of bias; if this is required, dextrose can be used in capsules.

In children less than 3 years of age the approach is somewhat different. If the history is impressive, a double-blind food challenge will be performed regardless of the results of the puncture skin test. In these situations skin testing is generally used to attempt to determine the mechanism responsible for any reaction that is produced. Mucosal biopsy is undertaken in those children having diarrhea in whom the etiology and/or pathogenesis cannot be determined.

TREATMENT

Avoidance

At present, the optimal method of treating symptomatic sensitivity to food is elimination of the offending food category from the diet. Very few children are sensitive to a multitude of foods in the diet, and when this occurs they can be fed an elemental diet (Nutramigen, Pregestimil, Vivonex) until their symptomatic sensitivity subsides. Children may be sustained for prolonged periods (months) on severely limited but nutritionally wholesome diets. For most children, the elimination of a single food is usually inconvenient but does not create an insurmountable problem for the family.

Drugs

Antihistamines, cromolyn sodium, and corticosteroids have been used to treat food sensitivity. It is my opinion that insufficient evidence is available to support the use of any of these drugs except for corticosteroids in intractable diarrhea of infancy.[22] Cromolyn has been shown to have some efficacy in certain situations[54]; however, it appears to have been unnecessary in any of the children treated at the National Jewish Hospital. In addition, there should be concern that while the clinical symptoms may be ameliorated, an immunologic and/or biochemical reaction may be occurring with potential long-term hazards.

Antihistamines have not been shown to be efficacious for use in subjects with food sensitivity and should not be used for this purpose until controlled studies have proven their utility.

Immunologic Manipulations

Current knowledge in immunology would allow the hypothesis that if specific antibody in the intestine (presumably of the IgA isotype) could be stimulated, then subjects with symptomatic sensitivity to foods might be protected by this antibody. Studies testing this idea have been performed in animals[6] but are far from being carried out in humans. Administering foods or extracts in small amounts orally or by injection are methods currently in vogue by some practitioners but have yet to be shown by scientific methods to have any validity. Attempts at "oral desensitization" or alteration of the immune response should currently be regarded as experimental. On the other hand, it may be appreciated that the stimulus-response relationship, as discussed earlier, supports the observation that a child may be able to ingest small amounts of an offending food whereas larger quantities evoke symptoms.

IMMUNOLOGY OF INFANT FEEDING

The immunology of breast milk and infant feeding has been reviewed in detail recently,[55,56] but a few comments seem warranted in a review of food sensitivity. A number of questions have been raised with regard to the immunologic response of the neonate and the content of the diet. Three will be considered here.

Does prolonged breast-feeding decrease the incidence of allergy, especially in children with a family history of atopy? This has been a controversial area for a number of years, with studies supporting both positive and negative answers. A recent study by Saarinen et al[57] in Finland presents evidence that prolonged breast-feeding (≥six months) decreased the incidence of symptoms of allergy in children who had a family history of allergy. All studies like this one have the problems of the continuance of long-term evaluation of subjects and of the influence that the loss of some subjects may have on the analysis of the data. Nevertheless, this is an area worthy of research pursuit because of its practical pertinence to every parent and every pediatrician.

What immunologic components does breast milk contain that may augment or influence the immunity of the infant? Breast milk has been shown by numerous investigators to contain antibodies to various substances, especially bacteria and viruses, macrophages, lymphocytes,

neutrophils, complement, and enzymes.[55,56] Most important from a sensitivity point of view is that breast milk can transmit antigenic material that would cause infants to have a clinically notable reaction. Studies at the National Jewish Hospital have identified children who have had GI, skin, and respiratory symptoms after their mothers have ingested foods.[15] Whether the protein is absorbed by the mother and transmitted intact to the infant or whether antigenic fragments are passed remains to be determined.

A study by Harris et al[58] has shown increased numbers of IgE-containing plasma cells in intestinal biopsy specimens of babies in whom colic was associated with milk ingestion. This controversial area requires further investigation and confirmation. At present, it seems premature to administer an elimination diet to every colicky infant; however, the physician should inquire about the possible onset of symptoms in relationship to feeding.

Does the level of IgE in umbilical cord sera predict the development of atopic symptoms? Studies by Dannaeus et al,[59] Orgel et al,[60] and Kjellman and Johansson[61] present data supporting the suggestion that elevated umbilical cord or serum IgE will be found more often in children in whom atopic symptoms eventually develop. The mechanisms whereby these findings occur require systematic investigation. Studies need to be designed to determine whether breast-feeding and/or low-antigen diets in the early months of life can be used in these children to reduce the later development of sensitivity reactions.

These and other questions, including determination of the incidence of sensitivity reactions to foods, are being investigated in numerous centers. The answers from this research should eventually help pediatricians and parents to better manage their children's diets.

COMMENT ON UNPROVEN SYNDROMES

There is currently a great deal more being written in the popular press for lay consumption on food allergy than is to be found in the medical literature. Clearly, many of the symptoms attributed to food allergy have nothing to do with the immune system. One of the most popular ideas is that "hyperactivity" is produced by food additives including some natural constituents and that it is produced by intake of sugar. All pediatricians should read carefully the studies by Harley et al,[62,63] which constitute the best attempts to date to study the Feingold hypothesis by using the scientific method. The issue of sugar and behavior has not been, to my knowledge studied scientifically; however, the patients seen at the National Jewish Hospital with this complaint all have very strong beliefs about how they will respond. In the few patients evaluated by use of double-blind challenge, the history has not been confirmed either during blind challenge or when the sugar is reintroduced into the diet in the incriminated form.

Certainly, pediatricians are plagued by these problems. Physician and layman alike should be encouraged to become more critical of sources that make sweeping claims without substantial support. It is definitely easier to blame a child's behavioral problems on the diet than it is to evaluate family interactions. This is true for both physicians and parents. One other problem in this field is the difficulty in achieving a universally accepted definition of hyperactivity.

The recent attention given to hyperactivity has tended to eclipse the other common but unsubstantiated diagnosis, namely, the tension-fatigue syndrome. Unfortunately, both of these groups of children have had their diet blamed for their problems, this being based on uncontrolled observations, anecdotal testimony, and empirically applied diets. It seems appropriate to repeat a statement first written elsewhere: "a drop of truth may rarely be tossed up from the depths of the sea of folly, but a dependable means is needed to pick out a drop of sense in a spray of nonsense. For this purpose the success of the scientific method places it well above empiricism."[64] The difficulty of applying the scientific method in certain situations does not absolve us from attempting its application to the best of our ability. Pressure from vocal groups with fervently held beliefs should not be the basis on which opinions and treatments are based by either the medical profession or regulating agencies. At present, most of these problems should be regarded as medical problems, not public health matters.

Finally, there are a number of unproven laboratory tests that are being regularly applied to patients with suspected adverse reactions to foods. These have been reviewed elsewhere and will not be repeated here.[65] Pediatricians should ask critical questions about interpretations of these tests when their patients are evaluated and treated by use of these methods.

CONCLUSIONS

In this review of food sensitivity, an attempt has been made to dispel some of the myth surrounding this subject. The important points to be remembered are that (1) an organized approach is available and has been listed if one takes the trouble to see that it is applied; (2) histories, even the most impressive ones, must be confirmed or refuted in an *unbiased, objective* manner before a diagnosis is made and a mechanism is sought; (3) there are currently useful laboratory techniques to aid in diagnosis of food sensitivity; and finally, (4) further research in this area is crucial for improving diagnostic tools, defining the mechanisms, and discovering an effective treatment or a method of prophylaxis.

Charles D. May, MD, provided guidance in the studies described herein. Linda Remigio provided technical assistance and, with Dr May and Georgia Wheeler, helped in the preparation of the manuscript.

Nonproprietary Name and Trademarks of Drug

Cromolyn sodium—*Aarane, Intal.*

References

1. May CD, Bock SA: A modern clinical approach to food hypersensitivity. *Allergy* 33:166-188, 1978.

2. May CD: Food hypersensitivity, in Gupta S, Good RD (eds): *Cellular, Molecular, and Clinical Aspects of Allergic Disorders*. New York, Plenum Press Inc, 1979, pp 321-354.

3. Rieger CHL, Rothberg RM: Development of the capacity to produce specific antibody to an ingested food antigen in the premature infant. *J Pediatr* 87:515-518, 1975.

4. May CD, Remigio LK, Feldman J, et al: A study of serum antibodies to isolated milk proteins and ovalbumin in infants and children. *Clin Allergy* 7:583-595, 1977.

5. May CD, Remigio LK, Bock SA: Usefulness of measurement of antibodies in serum in diagnosis of sensitivity to cow-milk and soy proteins in early childhood. *Allergy*, to be published.

6. Walker WA, Isselbacher KJ: Uptake and transport of macromolecules by the intestine: Possible role in clinical disorders. *Gastroenterology* 67:531-550, 1974.

7. Abrahamson DR, Powers A, Rodewald R: Intestinal absorption of immune complexes by neonatal rats: A route of antigen transfer from mother to young. *Science* 206:567-569, 1979.

8. Selbekk BH, Aas K, Myren J: In vitro sensitization and mast cell degranulation in human jejunal mucosa. *Scand J Gastroenterol* 13:87-92, 1978.

9. Owen RL: Sequential uptake of horseradish peroxidase by lymphoid follicle epithelium of Peyer's patches in the normal unobstructed mouse intestine: An ultrastructural study. *Gastroenterology* 72:440-451, 1977.

10. Rodricks JV: Food hazards of natural origin. *Fed Proc* 37:2587-2593, 1978.

11. Bock SA, Buckley J, Holst A, et al: Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy* 7:375-383, 1977.

12. Bock SA, Lee W-Y, Remigio L, et al: Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. *Clin Allergy* 8:559-564, 1978.

13. Parrish WE: Detection of reaginic and short-term sensitizing anaphylactic or anaphylactoid antibodies to milk in sera of allergic and normal persons. *Clin Allergy* 1:369-380, 1971.

14. Bryant DH, Burns MW, Lazarus L: Identification of IgG antibody as a carrier of reaginic activity in asthmatic patients. *J Allergy Clin Immunol* 56:417-428, 1975.

15. Bock SA, Lee W-Y, Remigio L, et al: Studies of hypersensitivity reactions to foods in infants and children. *J Allergy Clin Immunol* 62:327-334, 1978.

16. Strober W, Falchuk ZM, Rogentine GN, et al: The pathogenesis of gluten-sensitive enteropathy. *Ann Intern Med* 83:242-256, 1975.

17. Falchuk ZM, Gebbard RL, Sessoms C, et al: An in vitro model of gluten-sensitive enteropathy: Effect of gliadin on intestinal epithelial cells of patients with gluten-sensitive enteropathy in organ culture. *J Clin Invest* 53:487-508, 1974.

18. Falchuk ZM, Strober W: Gluten-sensitive enteropathy: Synthesis of antigliaden antibody in vitro. *Gut* 15:947-952, 1974.

19. Katz AJ, Falchuk ZM: Definitive diagnosis of gluten-sensitive enteropathy: Use of an in vitro organ culture model. *Gastroenterology* 75:695-700, 1978.

20. Falchuk ZM, Katz AJ, Shwachman H, et al: Gluten-sensitive enteropathy: Genetic analysis and organ culture study in 35 families. *Scand J Gastroenterol* 13:839-843, 1978.

21. Keuning JJ, Pena AS, van Hooff JP, et al: HLA-Dw3 associated with coeliac disease. *Lancet* 1:506-508, 1976.

22. Lloyd-Still JD, Shwachman H, Filler RM: Protracted diarrhea of infancy treated by intravenous alimentation: I. Clinical studies of 16 infants. *Am J Dis Child* 125:358-364, 1973.

23. Shwachman H, Lloyd-Still JD, Khaw K-T, et al: Protracted diarrhea of infancy treated by intravenous alimentation: II. Studies of small intestinal biopsy results. *Am J Dis Child* 125:365-368, 1973.

24. Savilahti E: Immunochemical study of the malabsorption syndrome with cow's milk intolerance. *Gut* 14:491-501, 1973.

25. Kuitunen P, Rapola J, Savilahti E, et al: Response of the jejunal mucosa to cow's milk in the malabsorption syndrome with cow's milk intolerance. *Acta Paediatr Scand* 62:585-595, 1973.

26. Shiner M, Ballard J, Brook CGD, et al: Intestinal biopsy in the diagnosis of cow's milk protein intolerance without acute symptoms. *Lancet* 2:1060-1063, 1975.

27. Walker-Smith J, Harrison M, Kilby A, et al: Cow's milk-sensitive enteropathy. *Arch Dis Child* 53:375-380, 1978.

28. Ament ME, Rubin CE: Soy protein: Another cause of the flat intestinal lesion. *Gastroenterology* 62:227-234, 1972.

29. Mendoza J, Meyers J: Soybean sensitivity: Case report. *Pediatrics* 46:774-775, 1970.

30. Mortimer CZ: Anaphylaxis following ingestion of soybean. *J Pediatr* 58:90-92, 1961.

31. Whitington PF, Gibson R: Soy protein intolerance: Four patients with concomitant cow's milk intolerance. *Pediatrics* 59:730-732, 1977.

32. Eastham EJ, Lichanco T, Grady MI, et al: Antigenicity of infant formulas: Role of immature intestine on protein permeability. *J Pediatr* 93:561-564, 1978.

33. Waldman TA, Wochner RD, Laster L, et al: Allergic gastroenteropathy: A cause of excessive gastrointestinal protein loss. *N Engl J Med* 276:761-769, 1967.

34. Wilson JF, Heiner DC, Lahey ME: Evidence of gastrointestinal dysfunction in infants with iron deficiency anemia: A preliminary report. *J Pediatr* 60:787-800, 1962.

35. Wilson JF, Lahey ME, Heiner DC: Further observations on cow's milk-induced gastrointestinal bleeding in infants with iron deficiency anemia. *J Pediatr* 84:335-344, 1974.

36. Katz AJ, Goldman H, Grand R: Gastric mucosal biopsy in eosinophilic (allergic) gastroenteritis. *Gastroenterology* 73:705-709, 1977.

37. Heiner DC, Sears JW, Kniker WT: Multiple precipitins to cow's milk in chronic respiratory disease. *Am J Dis Child* 103:634-654, 1962.

38. Holland NH, Hong R, Davis NC, et al: Significance of precipitating antibodies to milk proteins in the serum of infants and children. *J Pediatr* 61:181-195, 1962.

39. Lee SK, Kniker WT, Cook CD, et al: Cow's milk-induced pulmonary disease in children. *Acta Paediatr Scand* 25:39-57, 1978.

40. Anderson JA, Weiss L, Rebuck SW, et al: Hyperreactivity to cow's milk in an infant with LE and tart cell phenomenon. *J Pediatr* 84:59-67, 1974.

41. Boat TF, Polmar SH, Whitman V, et al: Hyperreactivity to cow milk in young children with pulmonary hemosiderosis and cor pulmonale secondary to nasopharyngeal obstruction. *J Pediatr* 87:23-29, 1975.

42. Aas K: The diagnosis of hypersensitivity to ingested foods: Reliability of skin prick testing and radioallergosorbent test with different materials. *Clin Allergy* 8:39-50, 1978.

43. Rothberg RM, Farr RS: Antibovine serum albumin and antialpha lactalbumin in the serum of children and adults. *Pediatrics* 35:571-588, 1965.

44. Gunther M, Cheek E, Matthews RH, et al: Immune responses in infants to cow's milk proteins taken by mouth. *Int Arch Allergy Appl Immunol* 21:257-278, 1962.

45. Kletter B, Gery I, Freier S, et al: Immune responses of normal infants to cow milk: I. Antibody type and kinetics of production. *Int Arch Allergy Appl Immunol* 40:656-666, 1971.

46. Gryboski JD: Gastrointestinal milk allergy in infants. *Pediatrics* 40:354-362, 1967.

47. Matthews TS, Soothill JF: Complement activation after milk feeding in children with cow's milk allergy. *Lancet* 2:893-895, 1970.

48. Spitzer RE, Stitzel AE, Urmson JR, et al: Utilization of properdin in children with vasculitis and milk allergy, abstracted. *Pediatr Res* 12:487, 1978.

49. Strunk RC, Pinnas JL, John TJ, et al: Rice hypersensitivity associated with serum complement depression. *Clin Allergy* 8:51-58, 1978.

50. Sandberg DH, Bernstein CW, McIntosh RM, et al: Severe steroid-responsive nephrosis associated with hypersensitivity. *Lancet* 1:388-391, 1977.

51. Bock SA, Remigio LK, May CD, et al: Detection of specific immunoglobulins and cow-milk proteins in small bowel biospies, abstracted. *Pediatr Res* 13:723, 1979.

52. Hekkens WTJM, Pena AS (eds): Coeliac Disease: Proceedings of the Second International Coeliac Symposium. Leiden, the Netherlands, HE Stenfert Kroese, 1974.

53. May CD, Alberto R: In vivo stimulation of peripheral lymphocytes to proliferation after oral challenge of children allergic to foods. *Int Arch Allergy Appl Immunol* 43:525-532, 1972.

54. Dannaeus A, Foucard T, Johansson SG: The effect of orally administered sodium cromoglycate on symptoms of food allergy. *Clin Allergy* 7:109-115, 1977.

55. Pittard WB III: Breast milk immunology: A frontier in infant nutrition. *Am J Dis Child* 133:83-87, 1979.

56. Welsh JK, May JT: Anti-infective properties of breast milk. *J Pediatr* 94:1-9, 1979.

57. Saarinen UM, Backman A, Kajosaari M, et al: Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* 2:163-166, 1979.

58. Harris MJ, Petts V, Penny R: Cow's milk allergy as a cause of infantile colic: Immunofluorescent studies on jejunal mucosa. *Aust Paediatr J* 13:276-281, 1977.

59. Dannaeus A, Johansson SG, Foucard T: Clinical and immunological aspects of food allergy in childhood: II. Development of allergic symptoms and humoral immune response to foods in infants of atopic mothers during the first 24 months of life. *Acta Paediatr Scand* 67:497-504, 1978.

60. Orgel HA, Hamburger RN, Bazaral M, et al: Development of IgE and allergy in infancy. *J Allergy Clin Immunol* 56:296-307, 1975.

61. Kjellman NI, Johansson SG: IgE and atopic allergy in newborns and infants with a family history of atopic disease. *Acta Paediatr Scand* 65:601-607, 1976.

62. Harley JP, Ray RS, Tomasi L, et al: Hyperkinesis and food additives: Testing the Feingold hypothesis. *Pediatrics* 61:818-828, 1978.

63. Harley JP, Matthews CG, Eichman P: Synthetic food colors and hyperactivity in children: A double-blind challenge experiment. *Pediatrics* 62:975-983, 1978.

64. May CD, Bock SA: Adverse reactions to food due to hypersensitivity, in Middleton E, Reed C, Ellis E (eds): *Allergy: Principles and Practice*. St Louis, CV Mosby Co, 1978, chap 62.

65. Golbert TM: A review of controversial diagnostic and therapeutic techniques employed in allergy. *J Allergy Clin Immunol* 56:170-190, 1975.

Special Feature

Radiological Case of the Month

Lionel W. Young, MD; Contributed by Marvin S. Kogutt, MD

An 830-g boy was born to a 17-year-old, primigravida mother after 27 weeks' gestation. At the time of delivery, he had no spontaneous respirations and was admitted to the Newborn Intensive Care Unit, Ochsner Clinic, New Orleans. He was intubated, and ventilation therapy was begun by bag; Apgar scores were 4 and 6 at one and five minutes. Severe respiratory distress was present with grunting, intercostal retractions, and decreased breath sounds bilaterally. The chest roentgenograms (Fig 1) were obtained at that time.

The infant was placed under a radiant warmer, and positive pressure ventilation therapy was begun with a respiratory rate of 16 per minute, a pressure of 20 cm H_2O, and a forced inspiratory oxygen of 75%. His condition remained relatively stable over the first 48 hours. However, respiratory distress continued to worsen, and he required increased respirator support. At 3 days of age, he became severely acidotic, but his condition subsequently stabilized and he required continuous high-pressure ventilation therapy. A chest roentgenogram (Fig 2) was obtained.

Over the next two days, the infant continued to require respirator support, and respiratory distress progressed. On the fifth day of life, he underwent sudden cardiovascular collapse with decreased breath sounds, and a friction rub was noted over the heart. Bradycardia and hypotension persisted in spite of attempts at resuscitation. A roentgenogram (Fig 3) was obtained immediately prior to the infant's death.

From the Departments of Radiology and Pediatrics, Ochsner Clinic, New Orleans.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr L. W. Young).

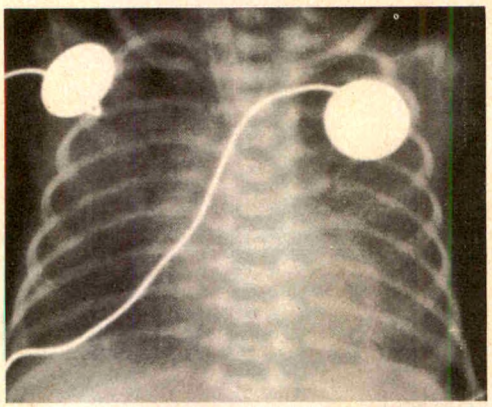
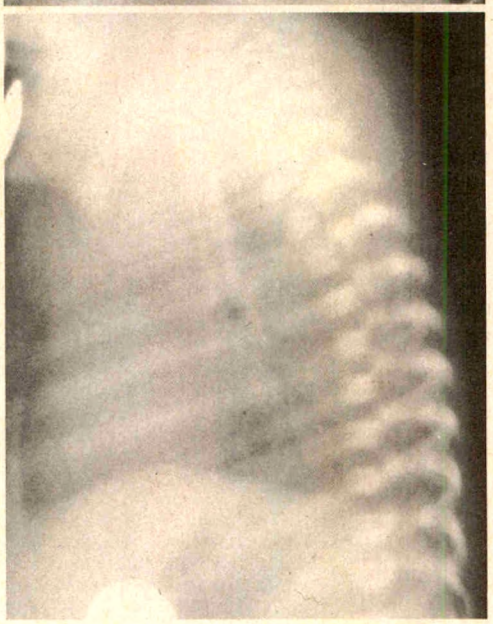


Figure 1.



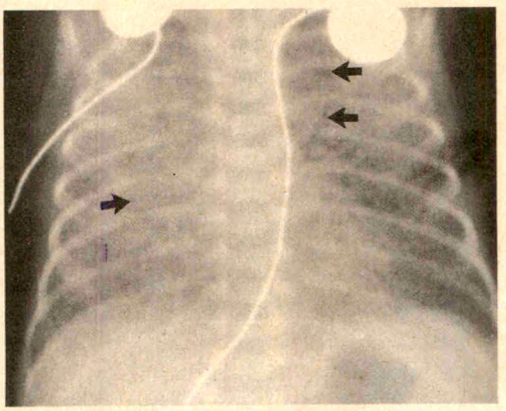


Figure 2.

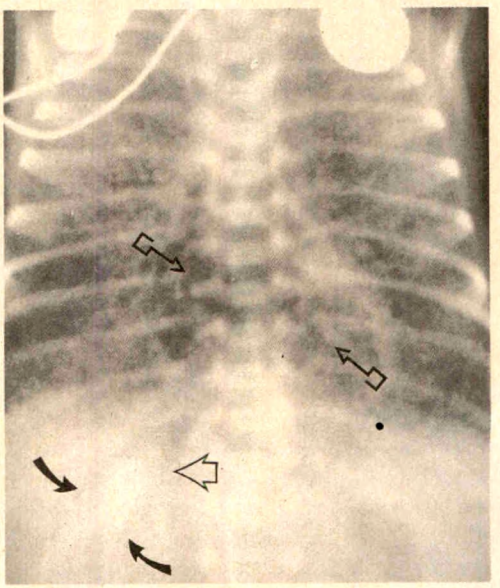


Figure 3.

Denouement and Discussion

Systemic Air Embolism Secondary to Respiratory Therapy

Fig 1.—Initial posteroanterior (top) and lateral (bottom) chest roentgenograms demonstrate bilateral reticulogranular pattern with peripheral air bronchograms and scattered punctate lucencies compatible with hyaline membrane disease/respiratory distress syndrome. Note endotracheal tube.

Fig 2.—Chest roentgenogram obtained at 3 days of age demonstrates linear, nonbranching lucencies extending into peripheral lung fields (arrows), indicative of pulmonary interstitial emphysema.

Fig 3.—Chest roentgenogram obtained at 5 days of age; preterminal. Air is present within cardiovascular system, including heart (broken arrows), hepatic veins (curved arrows), and inferior vena cava (open arrow).

Positive pressure ventilation is commonly used in the treatment of neonatal respiratory distress syndrome and is associated with an increased survival rate from the condition. Complications of positive pressure ventilation, specifically extra-alveolar and extrapulmonary air leaks, have become more frequent. Air-leak phenomena may result in a spectrum of abnormalities ranging in nature from clinically mild to severe and fatal.

The initial event is alveolar rupture. Air may then escape from the alveoli through the interstitial perivascular spaces and lung parenchyma to enter one or more potential spaces.[1-3] These may include the mediastinum, the pleura, the pericardium, the peritoneum, and the cardiovascular system. These spaces have the potential for communication, and any combination of these events may occur.[4,5]

The occurrence of systemic intravascular air embolism secondary to positive pressure ventilation usually, but not invariably, occurs as a late event in conjunction with other complications. Though the exact mechanism is unproven, the entrance of air into the vascular system most likely results from either the formation of alveolar-capillary or bronchovenous fistulae following alveolar rupture.[6-8] This may occur when the intra-alveolar exceeds the left atrial pressure, causing reversal of the normal pressure gradient with escape of air from the alveoli into the pulmonary veins.[7] Air may then travel directly to the heart and then into the systemic circulation.

The radiologic diagnosis is made by visualization of air within the systemic vascular circulation. Air is consistently and simultaneously present in both the arterial and venous circulations.[9,10] It is postulated that air enters the venous circulation through the capillary bed.[7] This venous air is consistently present in the hepatic veins. Intracardiac air is also a consistent finding and should be differentiated from pneumopericardium or pneumomediastinum. Postmortem roentgenograms to verify the presence of air should be interpreted with caution since rapid postmortem accumulation of gas is a frequent occurrence and may result in incorrect interpretation.[11]

The diagnosis of systemic air embolism is usually determined roentgenographically after severe clinical deterioration. With the widespread use of positive pressure ventilation, it is likely that systemic air embolism will become more frequent.

References

1. Macklin CC: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. *Arch Intern Med* 64:913-926, 1939.
2. Macklin MT, Macklin CC: Malignant interstitial emphysema of the lung and mediastinum as an important occult complication in many respiratory diseases and other conditions. *Medicine* 23:281-358, 1944.
3. Bowen FW, Chandra R, Avery GB: Pulmonary interstitial emphysema with gas embolism in hyaline membrane disease. *Am J Dis Child* 126:117-118, 1973.
4. Weller MH: The roentgenographic course and complications of hyaline membrane disease. *Pediatr Clin North Am* 20:381-406, 1973.
5. Mikity VG, Taber P: Complications in the treatment of the respiratory distress syndrome. *Pediatr Clin North Am* 20:419-431, 1973.
6. Chiu C, Golding MR, Linder JB, et al: Pulmonary venous air embolism: A hemodynamic reappraisal. *Surgery* 61:816-819, 1967.
7. Van Allen CM, Hrdina LS, Clark J: Air embolism from the pulmonary vein: A clinical and experimental study. *Arch Surg* 19:567-599, 1929.
8. Durant TM, Oppenheimer MJ, Webster MR, et al: Arterial air embolism. *Am Heart J* 38:481-500, 1949.
9. Shook DR, Cram KB, Williams JH: Pulmonary venous air embolism in hyaline membrane disease. *AJR* 125:538-542, 1975.
10. Vinstein AL, Gresham EL, Lim MO, et al: Pulmonary venous air embolism in hyaline membrane disease. *Radiology* 105:627-630, 1972.
11. Quisling RG, Poznanski AK, Roloff DW, et al: Postmortem gas accumulation in premature infants. *Radiology* 113:155-159, 1974.

Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD;

Contributed by John R. Pierce, MD, Gerald B. Merenstein, MD

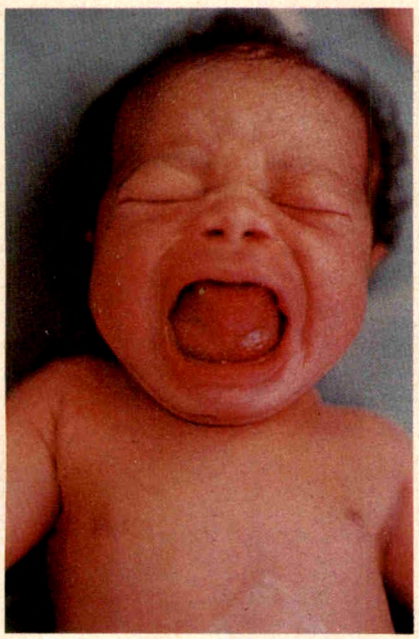


Figure 1.

Figure 2.

From the Newborn Service, Department of Pediatrics, Fitzsimons Army Medical Center, Denver.

Reprint requests to Boston Floating Hospital, 20 Ash St, Boston, MA 02111 (Dr Gellis).

Denouement and Discussion

Enteric Duplication Cyst

Fig 1.—Left and right, respectively, Enteric duplication cyst of tongue (at birth and age 8 weeks).

Fig. 2.—Transillumination of cyst.

Manifestations

Enteric duplications can occur anywhere along the alimentary tract. Most often found in the ileum, duplications have been reported to occur from the tongue to the anus. The duplication may be either tubular or cystic and is usually lined with mucosa similar to that of the adjacent alimentary tract structures; however, the mucosa may be similar to the more distant alimentary structures.

Enteric duplications occurring in the tongue are unusual, with, to our knowledge, less than ten cases reported. Manifestations, which are usually related to feeding difficulties, depend on the size of the lesion, the presence of communication with the oral cavity, compression of adjacent structures, and the presence of heterotopic mucosa. Respiratory embarrassment due to an enteric duplication cyst occurring in the tongue has not (to our knowledge) been reported. Although enteric duplications, in general, have a high incidence of associated anomalies (vertebral and gastrointestinal), no other anomalies have been reported in the published cases of duplications occurring in the tongue.

The differential diagnosis includes cystic hygroma, hemangioma, lymphangioma, ectopic thyroid, macroglossia, and rhabdomyoma. A thyroid scan should be performed to be certain that the infant's only thyroid tissue is not surgically removed.

Genetics

Enteric duplications do not appear to be inherited. There are several theories concerning their etiology, but none can explain the origin of all duplications. Of the theories proposed, persistence of fetal enteric diverticula would seem the most plausible for duplications occurring in the tongue.

Treatment

Careful surgical excision is the treatment of choice. If present at birth and not interfering with feeding or breathing, surgery can be postponed until symptoms occur. Concern over possible respiratory embarrassment is obvious; however, feeding difficulties usually precede any respiratory compromise.

References

1. Gorlin RJ, Kalnins V, Izant RJ: Occurrence of heterotopic gastric mucosa in the tongue. *J Pediatr* 64:604-606, 1964.
2. Lister J, Zachary RB: Cystic duplications in the tongue. *J Pediatr Surg* 3:491-493, 1968.
3. Favara BE, Franciosi RA, Akers DR: Enteric duplications. *Am J Dis Child* 122:501-506, 1971.

The Editors welcome contributions to "Picture of the Month" and "Radiological Case of the Month." Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

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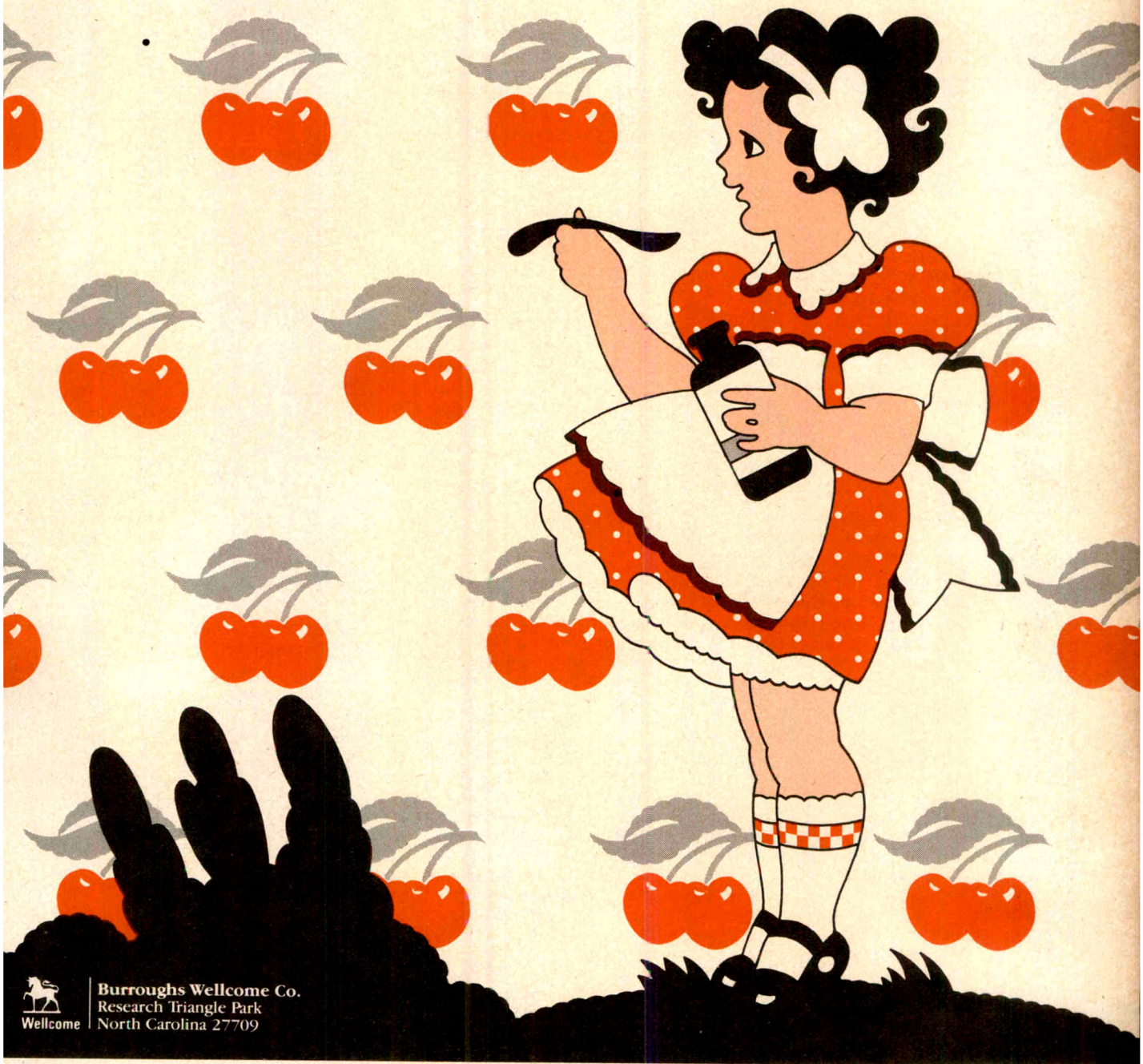

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Live-Born Triploid

Approximately 60% of all human spontaneous abortions during the first trimester of pregnancy are associated with chromosomal aberrations of the conceptus. Nearly 20% of these karyotypes are triploid,[1,2] ie, 66 autosomes and three sex chromosomes. Hence, triploidy is one of the most frequent chromosome aberrations in human abortuses.

Developmental arrest followed by spontaneous abortion of the triploid conceptus most often occurs between three and six weeks after fertilization[3]; however, there are reports (summarized in references 4 and 5) of 31 cases of full triploidy that survived past 24 weeks of gestation. In a recent study of nearly 60,000 consecutive live-born infants, only one was a triploid.[6] Though survival was usually limited to a few days[7] in the 11 reported cases of pure triploidy, Fryns et al[8] described a female infant who lived for two months after birth.

Triploid infants are reported to share a wide range of malformations; however, there is marked variability in the presence and/or expression of these anomalies. Even though no constellation of findings is pathognomonic,[9] the disorder can be suspected from clinical findings. This report describes a triploid male infant who lived for 14 hours after birth.

Report of a Case.—A 1,110-g male infant of 33 weeks' gestation was born to a 29-year-old, gravida 2, para 1 woman at St Luke's Hospital, Denver. The pregnancy was complicated by recurrent vaginal bleeding during the first trimester, poor fetal growth, and premature rupture of membranes at an estimated 32 weeks' gestation. Serial ultrasound examinations in the second and third trimesters corroborated the diagnosis of intrauterine growth retardation but failed to reveal any anomalies. The mother enjoyed good general health during the pregnancy and had not taken birth control pills in the preceding 12 months. She did not take alcohol, drugs, or medications, nor did she smoke. The father was 29 years old. Their first child was alive and well.

Attempts were made to inhibit labor by use of intravenous alcohol to allow transfer to Denver from her home in Nebraska, 200 miles away. Labor progressed, however, leading, 48 hours after membrane rupture, to delivery by cesarean section because of meconium-stained amniotic fluid and fetal bradycardia. The amniotic fluid volume was markedly reduced. The infant was depressed at birth and required a short period of positive pressure ventilation therapy with oxygen. Regular respirations were established in five minutes. Apgar scores were 2 and 6 at one and five minutes, respectively.

Clinical examination revealed the following: a growth-retarded, premature, male infant with craniofacial dysmorphism and other anomalies. Birth length was 37 cm (< tenth percentile), and birth weight 1,110 g (< tenth percentile). The cranial vault was large in relation to the face and body, and the occipitofrontal circumference measured 30.5 cm (45th percentile). The metopic suture was open to the glabella; other sutures were normal, but there was a large third fontanel. The scalp hair pattern was normal, and transillumination was within normal limits. There was an antimongoloid slant to the eyes, and, apart from the impression of a small nose, mouth, mandible, and tongue, these structures, the ears, and the remainder of the face and neck were normal.

The chest was small (circumference, 20.5 cm), with a marked thoracic scoliosis. The testes were not palpable, and a mild degree of glandular epispadias was present. The anus was patent, but the sphincter was lacking in tone. A right positional calcaneovalgus deformity was present. There was syndactyly of the third and fourth digits of all four limbs.

The infant demonstrated early respiratory distress, this being treated with oxygen. Spontaneous limb movements were present, but primitive reflexes (Moro's, grasp, root, and suck) were absent. A chest roentgenogram showed small hemithoraces consistent with pulmonary hypoplasia but no parenchymal disease. The scoliosis was evident. The cardiothymic silhouette was normal. The infant died in the next 14 hours of progressive respiratory failure.

Chromosome studies were done on peripheral blood lymphocytes obtained before death. Twenty cells were counted and all revealed a complete triploid karyotype, 69,XXY. No diploid cells were observed.

At autopsy, the brain weighed 300 g and had a normal gyral pattern for gestational age and no structural abnormalities. The thoracic cavity was small and cone-shaped. The left lung was bilobate and weighed 3.5 g; the unilobate right lung weighed 2 g. Microscopic examination revealed atelectasis, congestion, and amniotic squamocellular debris. The heart weighed 10 g and was normal.

Abdominal organs were in normal position and grossly unremarkable. Each kidney weighed 3.6 g; histologic findings were normal. Each adrenal gland weighed 0.4 g and consisted of about 90% fetal cortex. Two small testes were found in the pelvis.

The placenta weighed 170 g (fetoplacental ratio, 6.5) and was otherwise normal both grossly and microscopically. The umbilical cord was thin, with a single artery.

Comment.—The live birth of a nonmosaic triploid infant is a rare event. This is not surprising since there are arguments to suggest that a fetus will not survive if more than 5% of the haploid genome is triplicated.[10] Though there is no pathognomonic constellation of anomalies, live-born triploid infants show a number of common clinical stigmata and congenital malformations.[5,9,11,12]

The present case illustrates many of these, eg, first trimester bleeding; craniofacial anomalies including large posterior fontanel, low-set ears, and open metopic suture; syndactyly on all four limbs; adrenal hypoplasia; small penis; cryptorchidism; and intrauterine growth retardation. Our patient did not have cardiac, renal, or biliary tract anomalies. There was no omphalocele, abdominal organ abnormalities, spina bifida, or meningomyelocele.

In contrast to most other published cases, our patient had severe pulmonary hypoplasia, and the placenta was histologically normal. Oligohydramnios was diagnosed by ultrasonography ten weeks prior to delivery, and the small thorax observed at birth suggests that the hypoplastic lungs could have been the consequence of external compression of the thoracic cage resulting from the oligohydramnios. Since the pulmonary defect appears to be a deficiency of late fetal development,[13] it is unlikely that pulmonary hypoplasia would be reported in early triploid abortuses. Placental enlargement and/or hydatid

degeneration of the chorionic villi are often reported in triploidy; however, the placenta may be morphologically normal in term triploids.[9]

Theoretical mechanisms of origin of full triploidy have been extensively reviewed by Niebuhr[11] and include mitotic abnormalities in the germ cell precursors, errors in the first or second meiotic division of oocytes or spermatocytes, and dispermy. The origin of triploidy has been demonstrated in several cases by using various chromosome markers,[14] and it appears that two sets of paternal chromosomes are most frequently involved.[15]

There is no discernible effect of parental age. However, future pregnancies may be at increased risk for either polyploidy or aneuploidy. Boué and Boué[16] established the karyotypes of two consecutive spontaneous abortions in 43 women. One woman had two consecutive triploid abortuses, and eight others had triploid abortus each. Of these eight women, five had other abortuses with chromosomal anomalies, mostly autosomal trisomies. It would be interesting to know the frequency of chromosomal aberrations, especially complete and mosaic aneuploidy and polyploidy, in infants with nonrenal oligohydramnios.

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1. Boué J, Boué A, Lazar P: Retrospective and prospective epidemiological studies of 1,500 karyotyped spontaneous human abortions. *Teratology* 12:11-26, 1975.
2. Carr DH: Chromosome studies in selected spontaneous abortions: Polyploidy in man. *J Med Genet* 8:164-174, 1971.
3. Boué J, Philippe E, Giroud A, et al: Phenotypic expression of lethal chromosomal abnormalities in human abortuses. *Teratology* 14:3-20, 1976.
4. Bocian M, Karp LE, Mohandas T, et al: Intrauterine diagnosis of triploidy: The use of radiologic and ultrasonographic techniques in conjunction with amniocentesis. *Am J Med Genet* 1:323-332, 1978.
5. Wertelecki W, Graham JM, Sergovich FR: The clinical syndrome of triploidy. *Obstet Gynecol* 47:69-76, 1976.
6. Jacobs PA: Population surveillance: A cytogenetic approach, in Morton NE, Chung CS (eds): *Genetic Epidemiology*. New York, Academic Press Inc, 1978, pp 463-481.
7. Del Mazo J, Martínez González MA, Abrisqueta JA: Human triploid embryo: Cytogenetic and anatomopathologic study. *Hum Genet* 39:251-256,1977.
8. Fryns JP, van de Kerckhove A, Goddelris P, et al: Usually long survival in a case of full triploidy of maternal origin. *Hum Genet* 38:147-155, 1977.
9. Dudakov E, Perlman M, Ornoy A, et al: Triploidy in man: A clearly recognizable syndrome? *Isr J Med Sci* 13:493-499, 1977.
10. Sandler L, Hecht F: Genetic effect of aneuploidy. *Am J Hum Genet* 25:332-339, 1973.
11. Niebuhr E: Triploidy in man: Cytogenetical and clinical aspects. *Hum Genet* 21:103-125, 1974.
12. Fulton AB, Howard RO, Albert DM, et al: Ocular findings in triploidy. *Am J Ophthalmol* 84:859-867, 1977.
13. Thomas IT, Smith DW: Oligohydramnios, cause of the nonrenal features of Potter's syndrome, including pulmonary hypoplasia. *J Pediatr* 84:811-814, 1974.
14. Couillin P, Hors J, Boué J, et al: Identification of the origin of triploidy by HLA markers. *Hum Genet* 41:35-44, 1978.
15. Kajii T, Niikawa N: Origin of triploidy and tetraploidy in man: 11 cases with chromosome markers. *Cytogenet Cell Genet* 18:109-125, 1977.
16. Boué J, Boué A: Chromosomal analysis of two consecutive abortuses in each of 43 women. *Humangenetik* 19:275-280, 1973.

Milk Curd Obstruction Mimicking Necrotizing Enterocolitis

Intestinal obstruction in the newborn due to milk curds was first observed by Cook and Rickham[1] in 1969. The diagnosis has been confused with necrotizing enterocolitis (NEC).[2] A recent experience with an infant with milk curd obstruction who had clinical and roentgenographic evidence of NEC prompted this report.

Report of a Case.—An 880-g boy of 28 weeks' gestation was delivered vaginally after prolonged rupture of fetal membranes for more than 120 hours and administration of a course of betamethasone (12 mg/day for two doses) five days prior to delivery. Apgar scores of 8 and 4 at one and five minutes, respectively, led to bag and mask ventilation with 100% inspired oxygen. Initial problems included hyaline membrane disease that required prolonged mechanical ventilation, jaundice that required a double volume exchange transfusion, and seizures. Continuous feedings through a tube placed in the second portion of the duodenum consisting of commercially available formula (Similac LBW 24) were progressively increased until total enteral nutrition was achieved by the 13th day.

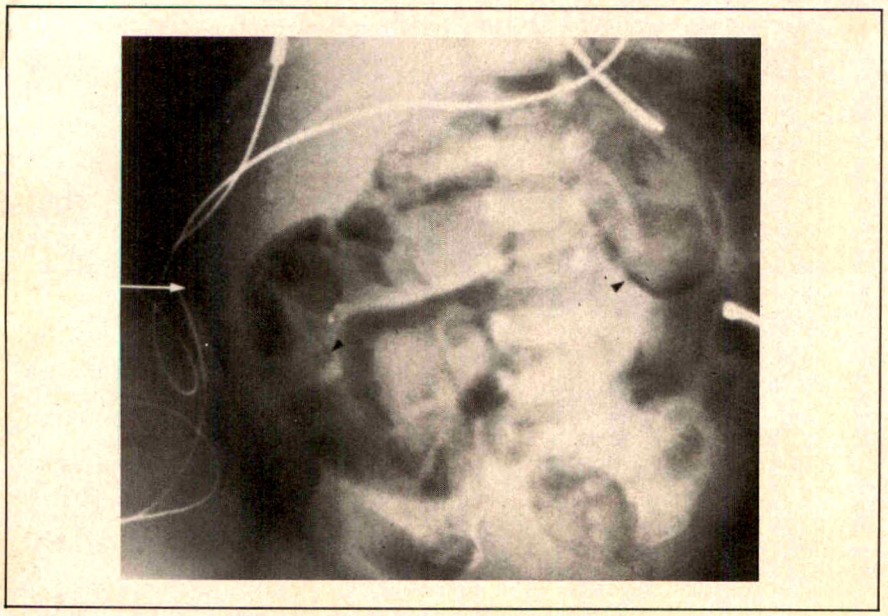
Apnea ultimately led to reinstitution of mechanical ventilation 19 days after birth. On the following day, dehydration was noted despite a fluid intake of 180 mL/kg/day. On day 22, abdominal distention and evidence of poor tissue perfusion accompanied roentgenographic evidence of pneumatosis. The initial roentgenogram was interpreted as showing possible free air (Figure).

A diagnosis of necrotizing enterocolitis with possible intestinal perforation was made. At surgery, the bowel appeared normal except for milk curds that obstructed the distal 30 cm of ileum. No perforation was found. An enterostomy was performed and the curds were removed. After a prolonged course complicated by recurrent apnea, the infant was discharged 99 days after birth with a weight of 1,780 g. No intestinal problems were noted in follow-up evaluation one month later.

Comment.—Milk curd intestinal obstruction has been reported in both term[3] and preterm[2,3,5] infants. Although considered unusual, it was reported by Dickson et al[6] to account for 17 of 238 neonatal intestinal obstructions over an eight-year period. Findings of abdominal distention and obstruction and dense intraluminal masses surrounded by a halo of air[4] have been described as characteristic clinical and roentgenographic features. Peritoneal air secondary to perforation has also been found.[1,4] Although infants as old as 6 weeks[7] and infants breast-fed during the first week[1] have been reported with the condition, the disorder is most common five to 14 days after birth in formula-fed infants.

The cause of this condition in the neonate is unclear. Cook and Rickham[1] suggested a relation to early provision of concentrated formula feeding accompanied by defective protein and amino acid absorption. Several recent reports describe lactobezoars in premature infants, all but one of whom were fed a special 800 calorie/L formula.[8,9] Schreiner et al[10] discussed several other potentially associated factors in these infants, and suggested that the condition is probably caused by multiple factors.

In the present case, a premature infant was fed an 800-calorie/L formula specifically designed to be given to low-birth-weight infants by continuous intraduodenal infusion. Abdominal distention and circulatory collapse, and roentgenograms that showed pneumatosis intestinalis, suggested the diagnosis of NEC. However, a milk curd obstruction was found at the



Anterior-posterior portable abdominal roentgenogram. Arrowheads indicate linear streaks in bowel wall interpreted as pneumatosis intestinalis. Large arrow indicates air in dilated bowel loop surrounding impacted milk curd.

time of laparotomy. Widespread use of concentrated formulas and transpyloric feedings may contribute to an increased incidence of obstruction of the intestine by milk curds. Since this condition may appear as NEC both roentgenographically and clinically with poor perfusion, efforts must be made to exclude this diagnosis. In retrospect, the onset of these signs in an infant who was tolerating intraduodenal feedings of this special low-birth-weight formula might well have alerted us to the correct cause. The reported roentgenographic finding of intraluminal air surrounding a milk curd, incorrectly interpreted as possible free air in this case, may be helpful in distinguishing milk curd obstruction from NEC.

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1. Cook RCM, Rickham PP: Neonatal intestinal obstruction due to milk curds. *J Pediatr Surg* 4:599-605, 1969.

2. Freidland GW, Rush WA, Hill AJ: Smythe's "inspissated milk syndrome". *Radiology* 103:159-161, 1972.

3. Pochon JP, Stauffer UG: Das Milchpfropfsyndrom. *Helv Paediat Acta* 33:53-57, 1978.

4. Cremin BJ, Smythe PM, Cywes S: The radiological appearance of the "inspissated milk syndrome", a cause of intestinal obstruction in infants. *Br J Radiol* 43:856-858, 1970.

5. Gravier L, Harper NE, Currarino G: Milk curd bowel obstruction in the newborn/infant. *JAMA* 238:1050-1052, 1977.

6. Dickson JAS, Lewis CT, Swain VAJ: Milk bolus obstruction of the neonate. *Arch Dis Child* 49:825, 1974.

7. Berman EJ, Ross C: Milk curd obstruction in a 6-week-old infant. *J Pediatr Surg* 7:342, 1972.

8. Erenberg A, Shaw RD, Yousefzadeh D: Lactobezoar in the low birth-weight infant. *Pediatrics* 63:642-646, 1979.

9. Duritz G, Oltorf C: Lactobezoar formation associated with high density calorie formula. *Pediatrics* 63:647-649, 1979.

10. Schreiner RL, Lemons JA, Gresham EL: A new complication of nutritional management of the low birth weight infant (editorial). *Pediatrics* 63:683-685, 1979.

Promethazine-Induced Acute Dystonic Reactions

Dystonic crises are usually associated with the antipsychotic phenothiazines. They are considered to be idiosyncratic reactions to phenothiazines as well as to other centrally acting agents such as the tricyclic antidepressants.[1] The phenothiazine group of drugs represents a variety of agents that differ in their pharmacologic effects. Promethazine hydrochloride is usually employed for its H_1 antihistaminic properties, and less frequently for its sedative-hypnotic effect. Some of its actions on the CNS have been ascribed to its potent anticholinergic activity.[2,3] Textbooks of pharmacology and poisoning suggest that promethazine, like all other phenothiazines, can produce acute dystonic reactions.[4] We found in the literature only one brief description of acute extrapyramidal manifestations caused by promethazine intoxication.[5]

Report of a Case.—A 2-year-old infant became lethargic after presumably ingesting promethazine syrup (Phenergan). An empty 240-mL bottle of the drug was found on the floor. She became unresponsive and difficult to arouse two to three hours later, and gastric lavage was performed about four hours after ingestion. This was associated with a brief respiratory arrest that responded to cardiopulmonary resuscitation. She gradually appeared to become less obtunded, but acute dystonic crises developed 24 hours after the ingestion of promethazine. Diphenhydramine hydrochloride (Benadryl) was given at that time to treat her oculogyric crises. She received 50-mg doses administered intravenously an hour apart, without effect. Twenty-eight hours after ingestion, the acute dystonic crises appeared to worsen, occurring every 30 to 60 s, with each episode lasting 15 to 20 s. Each would begin with a shrieking cry, followed by extension of the head and adversive head and eye turning, usually to the right side. This ocular turning was not obligate, since a positive response to the opposite side occurred when oculocephalic maneuvers were performed during the crisis. The defensive blinking to a visual threat during these episodes and the absence of pupillary dilation would indicate that this was not a convulsion. The left elbow was flexed and the right extended. She remained alert after these periods. As these dystonic movements subsided, stereotyped tongue-darting movements with lip smacking and repetitive sucking would continue for 5 to 10s. The crises ceased five hours after onset. Forty-eight hours after the ingestion, she was alert and her speech was normal. Her peripheral-muscle tone was increased and she had bilateral Babinski's signs that had resolved on subsequent follow-up examination after discharge.

A urine sample taken 28 hours after ingestion was assayed by the method of alkaline extraction followed by gas-liquid chromatography. It confirmed the presence of promethazine. An EEG performed 48 hours after the ingestion was normal.

Comment.—Previous reports of intoxication with promethazine described a total of five children, ranging in age from 5 to 11 years.[5-8] A depression in the state of conscious-

ness, generalized convulsions, and incoherence of speech were the commonly described effects of therapeutic doses on CNS function. In one case reported by Swaiman,[5] the patient had opisthotonic crises that resolved spontaneously. Twenty-eight hours after ingestion of promethazine, she was noted to have rhythmic jaw movements and coma. Our patient showed depression of the state of consciousness at the onset. The acute excitomotor manifestations developed as she became more alert. This is typical of intoxication with antihistaminic drugs.[2] However, oculogyric crises and orobuccolingual dyskinesias have not been described with anihistaminic agents.

The mechanism of such dystonic reactions is presently unclear. Some involuntary movements seen in acute dystonias resemble those occurring with chronic antipsychotic phenothiazine-induced tardive dyskinesia. It has been suggested that tardive dyskinesia may be a result of drug-induced supersensitivity of dopamine receptors after prolonged blockade.[2] The action of promethazine in the rat model differs from the antipsychotic phenothiazines and produces no change in the turnover of central dopamine hydrochloride.[9] But, in addition to its antihistaminic action, promethazine possesses considerable antiserotonin action, similar to LSD.[10]

It is possible that drug-induced dystonic reactions are a result of dopaminergic, cholinergic, or serotonergic blockade. The occurrence of acute dystonic crises, whether with antipsychotic phenothiazines or, as in our case, with promethazine, suggests that the mechanisms of production of acute reactions is different than that in tardive dyskinesia.

Drug-induced acute dystonic crises have been treated with various agents successfully, including diphenhydramine and benztropine mesylate. Fisher[6] used intramuscular diphenhydramine unsuccessfully to treat promethazine-induced combativeness, disorientation, and incoherence of speech in a child. He blamed the lack of response on the intramuscular route of administration. Our patient received intravenous diphenhydramine in adequate doses, with no apparent response. We did not use benztropine, since the rate of occurrence of the dystonic attacks appeared to be subsiding. Some authors suggest supportive management only, except if the patient's condition deteriorates.

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Nonproprietary Names and Trademarks of Drugs

Dopamine hydrochloride—*Intropin.*
Promethazine hydrochloride—*Fellozine, Ganphen, Phenergan.*

1. Lader MH: Drug-induced extrapyramidal syndromes. *J R Coll Physicians Lond* 5:87-98, 1970.
2. Burt DR, Creese I, Snyder SH: Antischizophrenic drugs: Chronic treatment elevates dopamine receptor binding in brain. *Science* 197:326-328, 1977.
3. Shearer CM, Miller SM: Promethazine hydrochloride. *Analytical Profiles of Drug Substances* 5:65, 1975.
4. Drug Therapy: Neurologic syndromes associated with antipsychotic-drug use. American College of Neuropsychopharmacology, Food and Drug Administration Task Force. *N Engl J Med* 289:20-23, 1973.
5. Swaiman KF: Acute neurologic reactions to promethazine. *N Engl J Med* 263:747, 1960.
6. Fisher SE: Encephalitic reaction to promethazine *J Pediatr* 80:896-897, 1972.
7. Gupta JM, Lovejoy FH: Acute phenothiazine toxicity in childhood. *Pediatrics* 39:771, 1967.
8. Waterhouse RG: Epileptiform convulsions in children following premedication to pamergan SP 100. *Br J Anaesth* 39:268-270, 1967.
9. Bunney BS, Walter JR, Roth RH, et al: Dopaminergic neurons: Effects of antipsychotic drugs and amphetamine on single cell activity. *J Pharmacol Exp Ther* 185:560-571, 1973.
10. Goth A: Antihistaminic drugs, in: *Medical Pharmacology*, ed 8. St Louis, CV Mosby Co, 1976, p 198.

Simultaneous Microangiopathic Hemolytic Anemia, Thrombocytopenia, and Acute Nephropathy in Mother and Child

Microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy are hallmarks of the hemolytic-uremic syndrome (HUS).[1] Though there have been reports of HUS occurring in families,[2-6] we are unaware of previous reports of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure occurring simultaneously in parent and child.

Report of Cases.—CASE 1.—A 31-year-old woman had been well until diarrhea and abdominal pain developed. Three days later, her stools became bloody, and she was admitted to the hospital.

Her initial hematocrit reading was 52%, and a few schistocytes were seen on blood smear. Platelets appeared adequate in number. The urine was concentrated, had ketones, but was otherwise normal. Her BUN and serum creatinine concentrations were 5.0 and 0.9 mg/dL, respectively. On the third hospital day, she became febrile, numerous purpuric lesions developed, and she became confused and lethargic. The platelet count fell to 40,000/cu mm, and the peripheral smear showed increased numbers of schistocytes. The hematocrit reading decreased rapidly, and several blood transfusions were given. The serum fibrinogen level was normal, but her serum tests were positive for fibrin split products. Her CSF was normal, blood cultures showed no growth, and no pathogens grew in stool cultures. A presumptive diagnosis of thrombotic thrombocytopenic purpura (TTP) was made, and she was treated with daily infusions of frozen plasma, dipyridamole, aspirin, and methylprednisolone (800 mg/12 hr). Two days later, she became anuric and comatose; frequent grand mal seizures developed, and ventilation therapy was begun. The following day, hemodialysis was begun, and fresh frozen plasma and platelet infusions were continued daily.

She remained comatose, thrombocytopenic, and anuric throughout the remainder of her hospitalization. Hemodialysis and artificial ventilation were continued, but the adult respiratory distress syndrome developed on the 18th hospital day, and she died ten days later. At autopsy, fibrin thrombi were found in the vessels of her kidney. A few scattered thrombi were also seen in her lung vessels, but the heart, intestines, stomach, liver, lymph nodes, adrenal glands, ovaries, and spleen were free of thrombi. The brain was not examined.

CASE 2.—The 4½-year-old son of patient 1 had cramping abdominal pain and bloody diarrhea the same day his mother became ill. The abdominal pain and bloody diarrhea persisted, and three days later he was admitted to the hospital.

The hematocrit reading was 40%, platelets appeared to be adequate in number, but occasional schistocytes were seen. His urinalysis results were normal, and the BUN concentration was 11 mg/dL. The cramping abdominal pain decreased substantially, though the bloody diarrhea continued. No pathogenic organisms grew in stool cultures, however.

A complete blood cell count done four days later revealed that the hematocrit reading had dropped to 15%, the serum hemoglobin level, to 5.0 g/dL, and the

platelet count, to 47,000/cu mm. His peripheral smear showed substantial numbers of schistocytes and occasional burr cells. The BUN concentration had increased to 49 mg/dL, and the urinalysis showed a trace of protein, RBCs (eight to ten per high-power field [HPF]), WBCs (five to ten per HPF), and casts (three to five per HPF). The child was transfused with packed RBCs. Three days later, the platelet count was up to 143,000/cu mm, the hematocrit reading was stable at 23%, and the BUN concentration was down to 13 mg/dL. He was discharged the following day. When seen in follow-up six months later, the child's hematocrit reading was 34%, the urinalysis results were normal, and the serum creatinine concentration was 0.7 mg/dL.

Comment.—Patients with HUS and TTP have many features in common. The enteritis, microangiopathic hemolytic anemia, thrombocytopenia, and acute renal disease experienced by the child fulfilled the criteria for the HUS. While his illness was milder than average, a wide range of severity is recognized.[7] His mother's persistent thrombocytopenia, microangiographic hemolytic anemia, severe neurologic involvement, and renal failure were characteristic for TTP. Histologic confirmation of multiple organ involvement was not found, however, and the few thrombi in the lungs could have been secondary to the adult respiratory distress syndrome. Her illness might, therefore, best be described as a severe case of HUS.

The reason for the occurrence of this disorder in both mother and child is uncertain. The simultaneous occurrence in both suggests a common environmental cause. Three days before they contracted enteritis, bloody diarrhea developed in the 2½-year-old male sibling of patient 2. He was otherwise asymptomatic, however, and the diarrhea resolved spontaneously within six days. Laboratory studies performed five days later showed no proteinuria, hematuria, or anemia. Though a variety of pathogens have been recovered from the stools of some patients with HUS, no enteric pathogens ever grew in cultures taken from our patients. Viral studies were not performed, however. The possibility of a genetic predisposition cannot be excluded, but Kaplan et al have speculated that genetically predisposed cases of HUS in siblings are characterized by disease episodes occurring more than a year apart.[2]

The report of the simultaneous occurrence of a hemolytic-uremic type syndrome in mother and child, coupled with previous reports of occurrence in families,[2-6] should alert physicians to consider this diagnosis in family members who share a similar diarrheal prodrome.

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Nonproprietary Name and Trademark of Drug

Dipyridamole—*Persantine.*

1. Kaplan BS, Thomson PD, de Chadarevian JP: The hemolytic uremic syndrome. *Pediatr Clin North Am* 23:761-777, 1976.
2. Kaplan BS, Chesney RW, Drummond KN: Hemolytic uremic syndrome in families. *N Engl J Med* 292:1090-1093, 1975.
3. Farr MJ, Roberts S, Morley AR, et al: The hemolytic uremic syndrome: A family study. *Q J Med* 44:161-188, 1975.
4. Karlesberg RP, Laecher JW, Bartecchi CE: Adult hemolytic-uremic syndrome. *Arch Intern Med* 137:1155-1157, 1977.
5. Hogewind BL, de la Riviere GB: A family with the hemolytic-uremic syndrome in childhood and in the postpartum period, abstracted. *Kidney Int* 11:222, 1977.
6. Blattler W, Wegmann W, Herold H, et al: Familiares hamolytisch-uramisches syndrom. *Schweiz Med Wochenschr* 105:1773-1774, 1975.
7. Dolislager D, Tune B: The hemolytic-uremic syndrome. *Am J Dis Child* 132:55-58, 1978.

Bilaterally Enlarged Testicles in a Newborn: An Atypical Presentation of Intrauterine Spermatic Cord Torsion

Torsion of the spermatic cord is a recognized surgical emergency at any age, but has peak incidence in the neonatal and adolescent pediatric age groups.[1] Perinatal unilateral torsion is well documented and the subject of a recent excellent review.[2] Bilateral intrauterine torsion of the spermatic cord, however, is a rare event—to our knowledge, only five cases have been reported.[3-7] We report a sixth case of intrauterine bilateral spermatic cord torsion with a markedly atypical presentation.

Report of a Case.—A 3,465-g full-term male infant was born to a 24-year-old, gravida 2, para 1, blood type O^+ mother after an uncomplicated pregnancy and labor. Meconium-stained amniotic fluid was observed at the time of vaginal delivery. There was no respiratory distress. Apgar scores were 6 at one minute and 9 at five minutes. Enlarged testicles were noted at delivery.

Physical examination revealed a full-term, appropriate for gestational age, male infant with a pendulous scrotum. There was no scrotal edema, swelling, puckering, or skin discoloration. The testes were enlarged bilaterally but not tender. The right testicle measured 1.5 × 2.5 cm (estimated volume, 2 mL). The left testicle measured 2.0 × 3.0 cm (estimated volume, 3 to 4 mL). Both testes were firm to palpation, slightly nodular, and did not transilluminate. The epididymis was located posteriorly bilaterally and the spermatic cords were of normal size. No other abnormalities were noted.

Laboratory results included a normal complete blood cell count and normal urinalysis results. Blood type was A^+ with a positive direct Coombs test for anti-A isoagglutinins. The serum bilirubin level was not elevated.

Consultations with specialists in pediatric oncology, endocrinology, genetics, urology, and pathology yielded many recommendations for additional laboratory tests. Electrolyte, T_4, and serum 17-OH-progesterone levels were normal. The serum testosterone level was 8 ng/dL (normal mean value, 68 ng/dL). A buccal smear was negative for Barr bodies. Karyotyping revealed a normal 46 XY chromosome pattern.

A scrotal roentgenogram showed no calcific densities. Doppler ultrasound examination of the testicular vessels revealed normal to slightly increased pulsations when compared with other male infants in the nursery. A technetium pertechnetate (Tc 99m) testicular scan indicated bilateral avascularity of the testes with a surrounding rim of increased uptake. The study was interpreted as consistent with tumor or bilateral torsion.

On the ninth day of life, reexamination revealed both testes to be slightly decreased in size (right, 1.9 × 2.2 cm; left, 2.0 × 2.6 cm). On the 11th day of life, the infant underwent surgical exploration of the scrotum and testicular biopsy. Dissection revealed inflamed, hemorrhagic tunicas and testes that appeared necrotic and atrophic. The right measured 1.2 × 0.7 × 0.8 cm and the left 1.5 × 0.7 × 0.8 cm. The diagnosis of bilateral extravaginal spermatic cord torsion was confirmed. Wedge biopsy specimens of both testes were obtained and the testes were repositioned in the scrotum; however, no improvement in blood flow was noted before closure.

Microscopic examination of the biopsy specimens showed the right testis to contain frank hemorrhagic necrosis with old pigment deposition of a chronic nature (Fig 1). The biopsy specimen from the left testis revealed markedly hemorrhagic tissue with many seminiferous tubules showing evidence of early hemorrhagic necrosis (Fig 2). These findings were consistent

with a disparity in time between torsion of the right and left testis, torsion of the right testis occurring first. Both torsions had occurred prior to birth.

Comment.—The present case is interesting in that the absence of acute local signs, ie, red or bluish skin discoloration, scrotal puckering, swelling, or edema, is an unusual presentation for testicular torsion. In addition, the right and left torsions appear to have occurred at different times in utero.

In light of the presumed torsion, the finding of good intrascrotal pulsations with a Doppler device was unexpected. Though arterial flow is usually decreased in torsion, increased Doppler pulsation has been reported in older patients with intravaginal torsion.[8] Whether a similarity in Doppler examination exists in patients with intravaginal and extravaginal torsion is not known. Technetium scanning of the testes is a relatively new but reportedly accurate method for evaluating testicular avascularity and has recently been advocated for use in young infants.[9] This method seems to provide a safe, rapid, and reliable adjunct to diagnosis. In the present case, a decrease in testicular perfusion was well demonstrated.

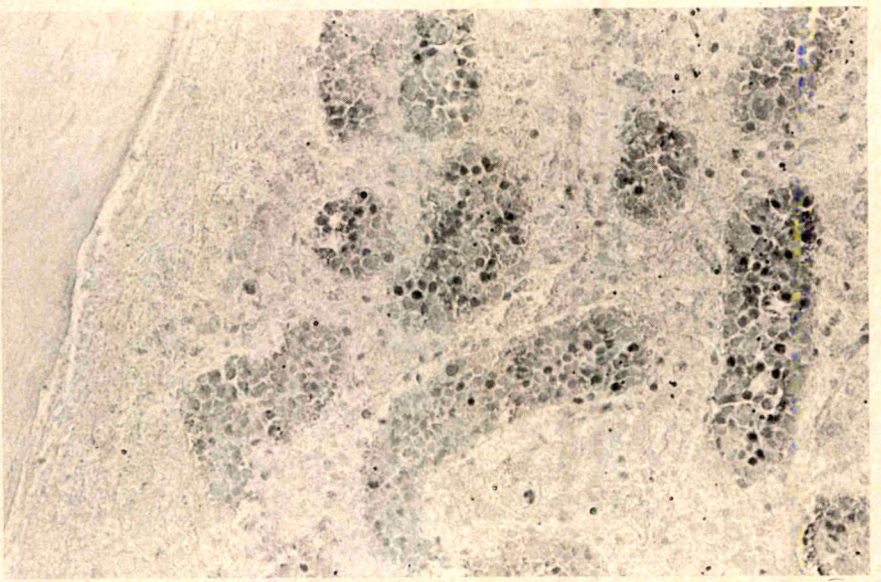

Fig 1.—Right testicular biopsy specimen. Hematoxylin-eosin stain reveals frank hemorrhagic necrosis of seminiferous tubules with hemosiderin deposition (×31.25).

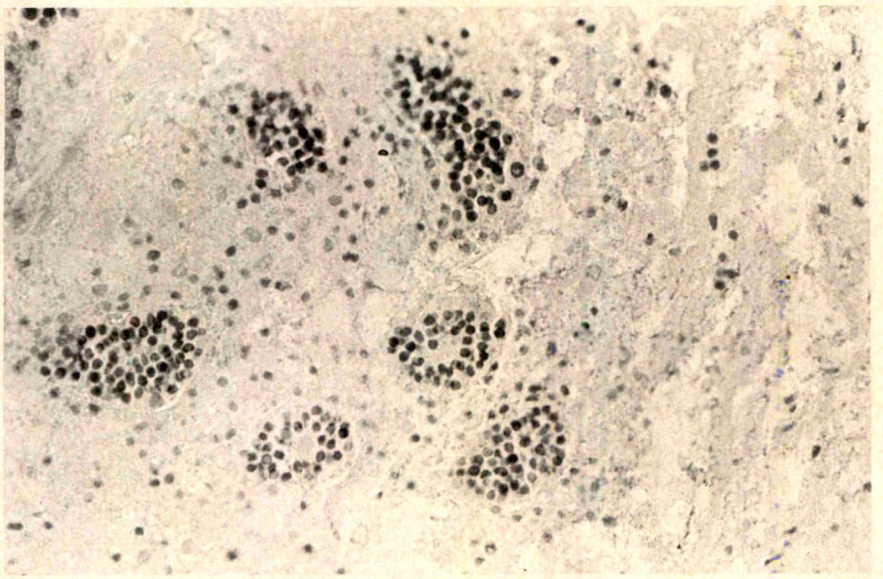

Fig 2.—Left testicular biopsy specimen. Hematoxylin-eosin stain shows marked hemorrhage with multiple seminiferous tubules evidencing early hemorrhagic necrosis (×31.25).

In comparing the present case with the five cases previously reported, it is noted that four of the six infants had either breech presentation, delivery by cesarian section, or presence of meconium at birth. All infants were asymptomatic. Five of the six infants had signs of acute torsion with scrotal swelling and skin color changes. Only three of 12 testes seemed to show reestablishment of some blood flow with surgical intervention. Of four cases where pathology reports are available, three show indications that right testicular torsion occurred at a time prior to torsion of the left side. This is particularly interesting, as left-sided torsion is more common in older patients. The predominance of right sided torsion preceding left may suggest a previously unrecognized etiological factor in extravaginal torsion.

Intrauterine bilateral spermatic cord torsion appears to represent a spectrum of disease. In earliest form, it occurs before or during testicular migration and results in childhood anorchia.[10] It may occur antenatally after migration (as in the present case), resulting in a lack of acute signs at birth. With occurrence at or near term, the more familiar signs of inflammation and ischemia will be present.

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1. Skoglund RW, McRoberts JW, Ragde H: Torsion of the spermatic cord: A review of the literature and an analysis of 70 new cases. *J Urol* 104:604-607, 1970.
2. Watson RA: Torsion of spermatic cord in neonate. *Urology* 5:439-443, 1975.
3. Frederick PL, Dushku N, Eraklis AJ: Simultaneous bilateral torsion of the testes in a newborn infant. *Arch Surg* 94:299-300, 1967.
4. Papadatos C, Moutsouris C: Bilateral testicular torsion in the newborn. *J Pediatr* 71:249-250, 1967.
5. Reid M, Graham WJH: Bilateral testicular torsion in the newborn. *Acta Paediatr Scand* 65:647-648, 1976.
6. Atallah MW, Ippolito JJ, Rubin BW: Intrauterine bilateral torsion of the spermatic cord. *J Urol* 116:128-129, 1976.
7. Zimmermann FA, Engert J, Meister P: Intrauterine doppelseitige hoden-torsion (Fallbericht). *Z Gebursthilfe Perinatol* 181:64-66, 1977.

8. Nasrallah PF, Manzone D, King LR: Falsely negative doppler examinations in testicular torsion. *J Urol* 118:194-195, 1977.

9. Datta NS, Tanaka T: Non-operative diagnosis of acute intrascrotal lesions. *J Pediatr* 92:862-863, 1978.

10. Aynsley-Green A, Zachmann M, Illig R, et al: Congenital bilateral anorchia in childhood: A clinical, endocrine and therapeutic evaluation of twenty-one cases. *Clin Endocrinol* 5:381-391, 1976.

'Breech Head' With Brow Presentation

Recently, Haberkern et al[1] described a group of newborns with scaphocephaly and occipital shelving that were sufficiently disfiguring to generate parental and physician concern. On the basis of a consistent association with breech positioning in utero in their series, they designated this the "breech head" and attributed it to a postural deformation related to this position or to sharing a common etiology.[1] We describe here an infant born with a classic breech head who was born in brow presentation.

Report of a Case.—A full-term, 3,347-g female infant was born to a 27-year-old primigravida. The pregnancy had been uncomplicated except for conversion of tuberculin in the second month, with a normal chest roentgenogram. Isoniazid therapy had been started in the seventh month. At no time had there been evidence of oligohydramnios. Labor had begun spontaneously and had been prolonged (26.5 hours). Delivery was difficult due to a brow presentation, with Apgar scores of 7 and 8 at one and five minutes, respectively. In the delivery room, the infant was noted to be hypotonic, scaphocephalic, and was thought to have dysmorphic facies. Genetic and neurologic consultation was sought in the nursery. Family medical history was remarkable only for three infant deaths and one miscarriage among maternal relatives. Physical examination revealed a hypotonic infant in no acute distress. Head circumference was 37 cm (98%) with marked scaphocephaly and occipital shelving. All sutures were normal to palpation, the anterior fontanel measuring 3 × 2.5 cm. The face was edematous with a large ecchymosis on the forehead. The nose was deviated slightly to the left. The mild dysmorphic features consisting of dystopia canthorum, broad and high nasal bridge, slightly low-set ears with depression of the superior helix, and a high-arched palate with unusual alveolar ridges did not suggest a specific dysmorphic syndrome. Results of the remainder of the examination were within normal limits. Skull roentgenograms confirmed the clinical impressions, showing elongation and shelving of the occiput (Figure). The karyotype was a 46,XX female pattern with normal Q-banding. The infant's tone improved and she was discharged home on the seventh day of life without a specific diagnosis other than that of breech head. Follow-up at 3 and 6 months of age in our clinic revealed a large, well-developed female infant whose head shape had reverted to normal. Results of developmental screening and neurologic examinations were within normal limits.

Lateral skull roentgenogram at birth showing scaphocephaly and occipital shelving.

Comment.—The clinical appearance and roentgenograms of this infant with brow presentation are identical to those described with the breech head. Haberkern et al[1] remarked that they had not excluded the occurrence of this deformation in other presentations. In the present case, the subsequent normal development and resolution of the deformation agree with similar observations of the postnatal natural history of infants with the breech head. The hypotonia in the neonatal period here may be attributed to the prolonged, difficult labor, which possibly in turn was influenced by the deformation. It is not clear whether this resulted exclusively from the prolonged labor or is related in some common pathway for this deformation in breech and other presentations. However, the association of altered tone and activity in utero has been correlated with the breech position[2] and may suggest some etiologic factors in common with our case. The possible role of this deformation in birth injuries from difficult vaginal deliveries has been emphasized by the original researchers,[1] and one week after the birth of the present patient, we saw an infant with the breech head in breech presentation who suffered a partial seventh nerve palsy before cesarian section was performed.

We conclude that whereas the strongest correlation with this deformation is the breech position in utero, other modes of compression clearly may likewise result in the breech head. We concur strongly with Haberkern et al[1] that early recognition of this may avert substantial birth trauma.

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1. Haberkern CM, Smith DW, Jones KL: The 'breech head' and its relevance. *Am J Dis Child* 133:154-156, 1979.

2. Braun FHT, Jones KL, Smith DW: Breech presentation as an indication of fetal abnormality. *J Pediatr* 86:419-421, 1975.

Hematemesis and Melena in Infant

Gastrointestinal (GI) hemmorrhage may be a serious symptom but in the newborn infant hematemesis and melena may simply be due to maternal blood swallowed during birth.[1-4] We report a case of apparently serious intestinal bleeding in a 10-week-old infant that turned out to be innocent.

Report of a Case.—The baby was born normally at term weighing 3,200 g and had no problems. She was breast-fed from birth and additional cow's milk and orange juice had been introduced. At the age of 10 weeks, she was referred to our pediatric emergency room by her attending physician because of melena and coffee-ground vomiting during a period of several hours. Apart from some reduction in appetite, she was otherwise behaving normally. On examination, she was surprisingly healthy with no pallor, tachycardia, or any other abnormal physical signs. Nevertheless, while being examined she vomited a small amount of coffee-ground material and passed a black stool that was strongly positive when tested for blood. Her hemoglobin level was 11.9 g/dL and her complete blood cell count was normal.

Because of the discrepancy between the excellent condition of the infant and the obvious blood in her GI tract, a thorough review of the history was made. Her mother denied administering any drugs and said she had no problems in breast-feeding. She had breast-fed her two previous children. Later, she admitted that the previous night she had experienced some discomfort

in feeding the infant and had noticed a small amount of blood on her nipple. A few hours after this, the infant had had her first melena and coffee-ground emesis. Examination of the mother by the pediatrician showed a deep fissure in her left nipple. Feeding from the left side was stopped and during the day the baby stopped vomiting and her stools became normal.

Comment.—The lesson to be learned from this case is the importance of the discrepancy between the clinical state of the infant and the presence of large amounts of blood in vomit and stool. As far as we are aware, ingestion of maternal blood has not been reported as a cause of hematemesis and melena in infants beyond the immediate neonatal period.

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1. Apt L, Downey WS Jr: Melena neonatorum: The swallowed blood syndrome. *J Pediatr* 47:6-12, 1955.
2. Brayton D: G.I. bleeding of 'unknown origin': A study of cases in infancy and childhood. *Am J Dis Child* 107:288-292, 1964.
3. Sherman NY, Clatworthy HW Jr: GI bleeding in neonates: A study of 94 cases. *Surgery* 62:614-619, 1967.
4. Spencer R: GI hemorrhage in infancy and childhood: 476 cases. *Surgery* 55:718-734, 1964.

Uridine Diphosphate Galactose 4-Epimerase Deficiency

In addition to the galactosemias associated with galactose-1-phosphate uridylyltransferase and galactokinase deficiency, uridine diphosphate (UDP) galactose 4-epimerase deficiency is a third disorder of galactose metabolism characterized by the inability to epimerize UDPgalactose and UDP-glucose. The first case was discovered during the course of newborn screening in Switzerland.[1] We would like to report observations on an infant whose condition was discovered in newborn screening and whose erythrocytes lack the capability to convert UDPgalactose to UDPglucose.

Patient and Methods.—The patient is the child of healthy parents. His blood was collected on filter paper for routine screening. Active uridyltransferase was indicated by the appearance of fluorescence in an enzyme spot screening test. The Paigen assay indicated a concentration of high levels of galactose and galactose-1-phosphate.[2,3]

At 3 months of age, he was referred to our hospital for the evaluation of the high level of galactose-1-phosphate in his blood. Epimerase activities were measured in heparinized blood from the infant, his parents, and adult control subjects by modifications of the method of Gitzelmann and Steinmann.[4] The blood galactose level was measured by the commercially available test combination based on oxidation by galactose dehydrogenase. The RBC galactose-1-phosphate level was measured by the same oxidation method with added alkaline phosphatase on filter-paper specimens. Galactose-1-phosphate uridylyltransferase activity was measured in a hemolysate by the UDPgalactose consumption method of Beutler and Baluda.[5]

Results.—Blood galactose-1-phosphate concentrations in the patient varied from 15 to 42 mg/dL during the first 7 weeks of life when he was receiving a lactose-containing formula. In our laboratory, the mean level of blood galactose-1-phosphate in 66 term infants at 5 to 7 days of life was 2.18 ± 1.55 mg/dL, with a range of 0 to 7.69 mg/dL. The normal range of blood galactose levels in neonates is 0 to 1.42 mg/dL.

At the age of 2 months, he was given an oral galactose tolerance test with 0.75 g/kg in 10% water. Blood galactose levels reached 11.0 mg/dL, and erythrocyte galactose-1-phosphate levels rose from 7.2 to 12.0 mg/dL after one hour. Epimerase activity in erythrocytes from the patient ranged between 0.076 and 0.310 μmole/hr/g hemoglobin.

The mean epimerase activity in the eight adults was 8.67 μmole/hr/g hemoglobin ±1.40 SD (range, 7.18 to 11.58 μmole/hr/g hemoglobin). The epimerase activities of his mother and father were 3.14 and 4.80 μmole/hr/g hemoglobin, respectively. He had normal activity of erythrocyte galactose-1-phosphate uridylyltransferase. No reducing substance was found in the urine. Results of his liver function tests were normal, and no cataracts or neurological manifestions were found.

After three months, he was fed with a formula containing less galactose, and his erythrocyte galactose-1-phosphate level was between trace and 5.0 mg/dL and fell to 0 mg/dL after galactose-free milk was instituted. His psychomotor development was normal at 1 year of age.

Comment.—The first case was discovered during a newborn screening program in Switzerland, and the patient's erythrocyte concentration of galactose-1-phosphate was found to be increased.[1] Eight persons in three different families are known to have no activity of UDPgalactose 4-epimerase in their circulatory blood cells.[6] Our data are in accordance with the findings of Gitzelmann et al[6] that led them to conclude that the epimerase-deficient state is a benign, inborn error of galactose metabolism.

There are no clinical or laboratory abnormalities in the epimerase-deficient person except for the slight increase of galactose and markedly increased concentrations of galactose-1-phosphate in peripheral blood. Lack of clinical findings is probably due to normal enzyme activities found in liver and some other tissues. Normal epimerase activities are found in cultured skin fibroblasts and stimulated lymphoblasts.[6] A correct diagnosis is mandatory to avoid unnecessary dietary treatment for the newborn infant with high levels of erythrocyte galactose-1-phosphate.

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1. Gitzelmann R: Deficiency of uridine diphosphate galactose 4-epimerase in blood cells of an apparently healthy infant: Preliminary communication. *Helv Paediatr Acta* 27:125-130, 1972.
2. Guthrie R: Mass screening for genetic disease. *Hosp Pract* 7:93-100, 1972.
3. Levy HL, Hammersen G: Newborn screening for galactosemia and other galactose metabolic defects. *J Pediatr* 92:871-877, 1978.
4. Gitzelmann R, Steinmann B: Uridine diphosphate galactose 4-epimerase deficiency: II. Clinical follow-up, biochemical studies, and family investigation. *Helv Paediatr Acta* 28:497-510, 1973.
5. Beutler E, Baluda MC: Improved method for measuring galactose-1-phosphate uridyltransferase activity of erythrocytes. *Clin Chim Acta* 13:369-379, 1966.
6. Gitzelmann R, Steinmann B, Mitchell B, et al: Uridine diphosphate galactose 4-epimerase deficiency: IV. Report of eight cases in three families. *Helv Paediatr Acta* 31:441-452, 1976.

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Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

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Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Recent studies of erythromycin reveal that its use in patients receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In such a case, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

See adjoining column for summary of prescribing information.

Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

Abdominal Pain

Sir.—I would like to comment regarding Dr Lebenthal's article "Recurrent Abdominal Pain in Childhood" (JOURNAL 134:347-348, 1980). As a clinician, I am repeatedly distressed to find that so many physicians who discuss abdominal pain find solace in the medical scrap basket called psychosomatic illness. I am sure that such problems are at times psychosomatic, but I believe that this diagnosis is made too frequently to mask our own inadequacies in diagnosis. The literature has shown repeatedly that foods can cause dramatic, observable effects on the gut and that these problems are real.[1-8] Not all food-related reactions are IgE-mediated. The fact that a physician cannot always understand *why* a food causes symptoms cannot be equated to the fact that a food *does* cause symptoms. Unfortunately, although careful clinicians see many children who respond favorably to dietary manipulation, scientific documentation is not always possible or practical. Parents who have been told repeatedly that they must accept their child's illness as nonorganic are grateful and relieved when they finally find a physician who readily eliminates the child's chronic intestinal problems within a few days by placing the child on a simple diet. Parents, however, are not so grateful that they want to be responsible for causing their children to have abdominal discomfort again merely to prove to some skeptical physicians that their child's medical problem was real. I do not think the parents can be faulted for this attitude.

In my experience, children who have dark circles about and puffiness under their eyes, a positive family and personal history of classic allergy, and recurrent abdominal pain often have a food-related problem. The symptoms frequently have started early in infancy with repeated formula changes, colic, inability to sleep, and repeated otitis. Affected children are often worse after parties or holidays; they are as ill on weekends as they are on school days, and many are better during the summer months. The latter is typical of some types of food-related allergies. Affected children often have associated chronic leg aches, muscle aches, enuresis, rhinorrhea, and activity, learning, and behavioral problems. These complaints are not psychosomatic; if left undiagnosed for many years, however, such problems surely arise on a secondary basis. This entity is Speer's[9] classic allergic-tension-fatigue syndrome. Unfortunately, this pediatric stepchild is often unsuspected or not diagnosed. A simple diet excluding the major highly allergenic foods for a week often relieves *all* of these symptoms, and by challenging the child with one food at a time during the second week, the individual symptoms often can be reproduced.[10] The relieving diet usually consists of meat (no bacon, ham, or luncheon meats), most fruits, and most vegetables (no corn). The diet excludes the major food offenders: milk, corn, sugar, wheat, eggs, chocolate, food coloring, food additives, and food preservatives. Somewhat less frequent offenders include orange juice, peanut butter, tomato, apple, and grape.

We live in an era of drug-oriented medicine. Maybe it is time we started to listen to parents, to seriously consider their observations, and to realize that what we put into the gastrointestinal tract could, conceivably, adversely affect any area of the body.[11]

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1. Duke WW: Food allergy as a cause of abdominal pain. *Arch Intern Med* 28:151-165, 1921.
2. Rowe AH: Gastrointestinal allergy. *JAMA* 97:1440-1444, 1931.
3. Rowe AH: Roentgen studies of patients with gastrointestinal food allergy. *JAMA* 100:394-400, 1933.
4. Fries JH, Zizmor J: Roentgen studies of children with alimentary disturbances due to food allergy. *Am J Dis Child* 54:1239-1251, 1937.
5. Fries JH, Mogil M: Roentgen observations on children with gastrointestinal allergy to foods. *J Allergy Clin Immunol* 14:310-321, 1943.
6. Fries JH: Roentgen studies of allergic children with disturbances of the pylorus resulting from food sensitivity. *J Allergy Clin Immunol* 23:39-47, 1952.
7. Pollard HM, Stuart GJ: Experimental reproduction of gastric allergy in human beings with controlled observations on the mucosa. *J Allergy Clin Immunol* 13:467-473, 1942.
8. Gray I, Harten M, Walzer M: Studies in mucous membrane hypersensitiveness: IV. The allergic reaction in the passively sensitized mucous membranes of the ileum and colon in humans. *Ann Intern Med* 13:2050-2056, 1940.
9. Speer F: Allergic tension-fatigue in children. *Ann Allergy* 12:168, 1954.
10. Rapp DJ: *Allergies and Your Family.* New York, Sterling Publishing Co Inc, 1980.
11. Soothill JF: Elimination diets in childhood. *Br Med J* 280:401-402, 1980.

Mortality and Sex Difference

Sir.—In a recent article entitled "Immunological Bases for Superior Survival of Females" (JOURNAL 133:1251-1253, 1979), Purtilo and Sullivan presented evidence for superior immunocompetence of females and hypothesized that this contributes to the greater longevity of females. It is useful to consider their argument in the context of a more comprehensive analysis of the causes of sex differences in mortality.[1]

In the contemporary United States, sex differences in mortality due to infectious diseases account for only about 4% of the total sex difference in mortality (based on age-adjusted death rates calculated from data in *Vital Statistics of the United States*[2] using methods described by Waldron[1]). Sex differences in mortality due to neoplasms account for an additional 14% of the total sex difference in mortality. It is unclear how much of this difference may be due to sex differences in immunocompetence. It should be noted that malignant neoplasms of the respiratory system alone are responsible for 11% of the total sex difference in mortality, and it is clear that in this case sex differences in cigarette smoking habits make a major contribution to the sex differences in mortality.[1-3]

Forty-one percent of the total sex difference in mortality is due to ischemic heart disease. Previous analyses have presented evidence that men's higher rates of ischemic heart disease are due in large part to greater cigarette smoking by men,[1,3,4] a greater prevalence of the hard-driving "Type A" or Coronary-prone Behavior Pattern among men,[1,4,5] and possibly also to the effects of sex hormones.[1,4,6]

Other causes of death that contribute to the sex difference in mortality include accidents (11% of the total difference), homicide and suicide (5%), and emphysema and cirrhosis of the liver (5%). In each case, sex differences in behavior make a substantial contribution to the sex differences in mortality.[1]

There is considerable cross-cultural and historical variation in the sex differences in mortality.[1,4,7] For example, in the United States, the sex difference in life expectancy was eight years in 1970, but only two years in 1920.[1] Analyses of the historical and cross-cultural variation have provided further evidence that behavioral and cultural factors make a major contribution to sex differences in mortality.[1,4,7]

In conclusion, although sex differences in immunocompetence probably contribute to sex differences in mortality, the available evidence indicates that sex differences in behavior make a substantially larger contribution to sex differences in mortality in the contemporary United States.

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1. Waldron I: Why do women live longer than men? *Soc Sci Med* 10:349-362, 1976.
2. *Vital Statistics of the United States, 1973, Vol II—Mortality*. US Dept of Health, Education, and Welfare, 1977.
3. *Smoking and Health: A Report of the Surgeon General*. US Dept of Health, Education, and Welfare, 1979.
4. Waldron I: Sex differences in longevity, in Haynes SG, Feinleib M (eds): *Proceedings of Second Conference on Epidemiology of Aging*. Bethesda, Md, National Institute of Aging, to be published.
5. Waldron I: Sex differences in the coronary-prone behavior pattern, in Dembroski TM, Weiss SM, Shields JL, et al (eds): *Coronary-prone Behavior*. New York, Springer-Verlag, pp 199-205, 1978.
6. McGill HC, Stern MP: Sex and atherosclerosis. *Atherosclerosis Rev* 4:157-242, 1979.
7. Preston SH: *Mortality Patterns in National Populations*. New York, Academic Press Inc, 1976, pp 120-162.

Reye's Syndrome

Sir.—I read with interest the article in the JOURNAL (133:1009-1013, 1979) by Baliga and co-workers, who described three patients with Reye's syndrome associated with disseminated intravascular coagulation (DIC) and acute renal failure. The authors emphasized the importance of initial and continuing evaluation of renal function in Reye's syndrome, especially in patients receiving osmotic diuretic therapy.

I would like to stress another point. All patients received fresh frozen plasma because of a severe coagulopathy compatible with DIC. The coagulopathy did not improve after administration of the coagulation factors and, subsequently, exchange transfusions were done. Thrombocyte counts were near normal on admission to the hospital but decreased during the course of the disease.

Administration of plasma and plasma products, in particular prothrombin complex concentrates, can induce or accentuate DIC with liver disease.[1-5] In 1977, Grubbauer and I described an infant with severe Reye's syndrome in whom DIC and renal failure also developed.[6] This patient was admitted to our hospital with a normal thrombocyte count. Because of the prolonged prothrombin time, a prothrombin complex concentrate was administered. Subsequently, the platelet count dropped to low levels, and coagulation studies showed signs of severe DIC. At this point, the infant was heparinized, and the coagulation profile gradually returned to normal. However, renal dysfunction persisted, and a fatal outcome could not be averted.

Administration of coagulation factor-containing material to patients with Reye's syndrome should be done cautiously and with careful monitoring of clotting tests. If signs of hypercoagulability or DIC develop or persist, judicious use of heparin should be considered. In certain cases of liver disease associated with DIC, heparin has been demonstrated to be of benefit.[1,4]

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2. Brunswig D, Liehr H, Richter E: Verbrauchskoagulopathie bei toxischer Leberschadigung durch Knollenblatterpilzvergiftung. *Dtsch Med Wochenschr* 97:1347-1354, 1972.
3. Preston FE, Winfield DA, Malia RG, et al: Serial changes in the coagulation system following clotting factor concentrate infusion. *Thromb Diathes Haemorrh* 34:475-482, 1975.
4. Verstraete M, Vermylen J, Collen D: Intravascular coagulation in liver disease. *Ann Rev Med* 25:447-455, 1974.
5. Oka K, Tanada K: Intravascular coagulation in autopsy cases of liver disease. *Thromb Haemost* 42:564-570, 1979.
6. Muntean W, Grubbauer HM: Disseminierte intravasale Gerinnung beim Reye-Syndrom. *Wien Klin Wochenschr* 89:58-61, 1977.

Genetic Implications of Ultrasonographic Detection of In Utero Cystic Hygroma

Sir.—In a recent RADIOLOGICAL CASE OF THE MONTH (JOURNAL 134:311-312, 1980), a cystic nuchal mass interpreted as a hygroma was detected by ultrasonography in a fetus of 28 weeks'

gestation. The full implications of the antenatal detection of hygroma by ultrasonography should be emphasized.

Chromosomal anomalies are probably responsible for a high percentage of spontaneous abortions and fetal deaths.[1] Cystic hygroma of the back of the neck is responsible for the webbed neck seen in stillborn and newborn infants with XO karyotypic Turner's syndrome. The appearance of the stillborn infant illustrated in the aforementioned case is strongly suggestive of that diagnosis.[2] The cleft lip/palate not associated with hygroma described in the previous stillborn infant also may be seen in Turner's syndrome, but neither those findings nor hygroma are sufficient to make that diagnosis in the absence of other pathologic findings or a karyotype. The posterior hygroma should also be distinguished from the more common anterolateral and often unilateral hygroma colli, which may be present at birth as an isolated lesion. The history of prior abortion and two stillbirths in the report suggests the possibility of a recurrent syndrome associated with fetal wastage, such as the familial nuchal bleb syndrome described in a karyotypically normal abortus.[3]

We suggest that abnormalities detected by ultrasonography be corroborated and extended by definitive cytogenetic and pathologic studies of aborted or stillborn infants. Supported by definitive information from combined studies, the physician may knowledgeably counsel the parents concerning past and future pregnancies.

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2. Warkany J: *Congenital Malformations*, ed 1. Chicago, Year Book Medical Publishers, 1971, pp 1122-1136.

3. Bieber FR, Petres RE, Bieber JM, et al: Prenatal detection of a familial nuchal bleb simulating encephalocele, in Golbus MS, Hall BD (eds): *Diagnostic Approaches of the Malformed Fetus, Abortus, Stillborn, and Deceased Newborn*. Birth Defects original article series, New York, Alan R Liss Inc, 1979, vol 15, No. 5A, pp 51-61.

In Reply.—We agree with Drs Rutledge and Haas that Turner's syndrome has to be ruled out in a patient with evidence of hygroma. We raised the possibility of Turner's syndrome in our report and recommended amniocentesis because of the increase of α-fetoprotein in the fluid of fetuses with Turner's syndrome, though some believe that this is due to obtaining fluid from the cervical sac rather than from amniotic fluid.

As far as genetics is concerned, a majority of patients with Turner's syndrome are 45,X. However, 20% to 30% have various types of mosaicism including X/XX, X/XY, and X/XX/XY, or structurally altered chromosomes, such as an isochromosome X, ring X, or partial deletion of the X chromosome. No chromosomal analysis of amniotic fluid was done on our patient. A chromosomal study was attempted in the stillborn infant, but due to maceration of the fetal tissue the study was not successful.

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Advertising Condoms

Sir.—The article, "Condoms for Sexually Active Adolescents" by Bergman (JOURNAL 134:247-249, 1980), deserves some comments. Advertising in the public media via television, radio, newspapers, and magazines may arouse the curosity of preteenagers unnecessarily and contribute to sexual activity in this age group. Advocating sexual responsibility and downplaying sexual activity before marriage may be a better way to prevent disease and unwanted pregnancies. If you really want to reach the teenagers, why not have condom dispensers in the boys' and girls' washrooms in the high schools? This would eliminate the embarrassment of buying condoms over the counter in drug stores and ensure availability for sexually active adolescents at a nominal price. I can well imagine the typical school board's and parents' response!

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Sir.—In his article, Bergman has some persuasive arguments for encouraging the use of condoms by sexually active adolescents. I would, however, take issue with his approach. He advocates mass advertisement of condoms on television and radio and in newspapers and magazines. Does this mean that when you "go for the gusto," you reach for a condom or that two Wheaties box tops will get you a rubber? Probably not. However, the American advertising industry can take an item like a condom, glorify it, strip it of its moral implications, and make it as necessary for every teenager as underarm deodorant.

We believe that this mass-media approach implicitly establishes a moral standard and legitimizes teenage sexual activity. Dr Bergman states, "by advocating condom usage to those who are already sexually active, the physician does not condone promiscuity." This is, of course, true; but what about sexually inactive adolescents, and the parents who attempt to rear teenagers with sexual restraint? Might this not be an additional pressure similar to pornographic literature and movies?

Our alternative would be to zero in on the target group rather than the teenage populace at large. This could begin with general education programs in the schools, followed by distribution in commercial outlets that are keyed to the subculture of sexually active teenagers.

We agree that we must take tangible steps to mitigate the problem of teenage pregnancies and venereal disease. At the same time, let's not neutralize our moral principles so as to make "promiscuous" an obsolete word.

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In Reply.—The concerns expressed by Drs Feroli and Mella are legitimate and well stated. It is possible that certain types of sensational contraceptive advertising might tempt previously chaste youngsters to "cross the line." It is hard for me to imagine, however, how ads for contraceptives could be any more "suggestive" than the material that currently saturates our television and movie screens. It has been repeatedly shown that

knowledge about sexuality does not alter sexual behavior.[1] The vast majority of youngsters who come to physicians' offices and family planning clinics inquiring about contraception are already sexually active.[2] Where is the target group that is sexually active? Assuredly not restricted to poor ghetto areas, but in my experience, omnipresent.

I agree with Dr Friday that we must continue to advocate sexual responsibility, but won't he cede, given that one of ten teenagers are becoming pregnant, that some different tack is needed? Pounding the pulpit harder is not going to do the job.

Whatever our thoughts about availability of contraceptives, cannot all members of the medical profession agree on the goal of reducing teenage pregnancies? If so, we should all support health education programs from kindergarten through 12th grade that stress responsible family life. I do not blame parents or school boards for banning discussions of human sexuality if physicians do not point out the costs of such a "head-in-the-sand" attitude. For my part, since a means is at hand to prevent numerous cases of hyaline membrane disease, sudden infant death syndrome, child abuse, and wretched parenting, I want at least to make the effort.

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1. Spanier GB: Sex education and premarital sexual behavior among American college students. *Adolescence* 13:659-674, 1978.

2. Akpom CA, Akpom KL, Davis M: Prior sexual behavior of teenagers attending rap sessions for the first time. *Fam Plann Perspect* 8:203-206, 1976.

Spondylohypoplasia, Arthrogryposis, and Popliteal Pterygium

Sir.—We read with interest the report of Turkel et al in the JOURNAL (134:42-45, 1980) on a malformation complex that included spondylohypoplasia, arthrogryposis, and popliteal pterygium. We recently evaluated the condition of a male infant with the same characteristics. We believe that our description will add some observations to the already described anomalies and assist in recognition of this new malformation complex.

Report of a Case.—A term, male infant was born by cesarean section to a 22-year-old gravida 2, para 2, Puerto Rican mother. The father is a 23-year-old Puerto Rican. The marriage is nonconsanguineous. Their first child is a healthy 2½-year-old boy. There was no history of illness or drug ingestion during pregnancy. The birth weight was 2.830 g.

At birth the following features were noted: head hyperextension, wide anterior fontanel, faint frontal nevus flammeus, mild ocular proptosis, palpebral ptosis, high-arched palate, short neck, arthrogryposis, bilateral incomplete palmar simian creases, finger knuckle crease absence, short trunk, protuberant abdomen, discrete umbilical hernia, lordosis, hip abduction absence, popliteal pterygium, overlapping second toes, and rocker bottom feet.

At age 3 days, the infant had several brief episodes of cyanosis and tachycardia, tachypnea with a single snappy second heart sound, and hepatomegaly developed. The ECG showed sinus tachycardia, right deviation of the QRS axis, and upright T waves over the right precordial leads. The chest roentgenogram showed numerous vertebral anomalies, abnormal orientation of ribs, cardiomegaly, and normal pulmonary vascularity.

Treatment with digoxin and oxygen resulted in marked improvement. At age 14 days, his second heart sound was narrowly split but the ECG showed the same characteristics. At age 3 months, the cardiac auscultation and the ECG were entirely normal.

Comment.—A delay in the fall of pulmonary vascular resistance and pressure (probably enhanced by the thoracic deformity) precipitated cardiac insufficiency in this baby. As soon as the pulmonary hemodynamics improved, all the abnormal cardiovascular findings disappeared. We believe that these constellations of anomalies are gaining validity as a new syndrome.

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'Fever Phobia'

Sir.—Dr Barton Schmitt's excellent article "Fever Phobia" in the February JOURNAL (134:176-181, 1980) is must reading for medical students and house officers, as well as a good reminder for practitioners. His guidelines might be improved on by initiating the discussion of fever with parents at the infant's first diptheria toxoid, pertussis vaccine, tetanus toxoid injection, rather than at the 4- or 6-month visit. Over the past 25 years I have found this a most opportune time to begin the "desensitization" program.

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Child Abuse

Sir.—We find interesting comparisons between the data of Ellerstein and Canavan (JOURNAL 134:255-257, 1980) and the experience of our institution's Child Protection Committee. The committee reviews cases of all patients seen at Oklahoma Children's Memorial Hospital, Oklahoma City, who are suspected of being abused, regardless of their initial complaint. Thus, in contrast to the study population of Ellerstein and Canavan, ours includes patients first seen with complaints often entirely unrelated to sexual abuse.

Our overall proportional experience with cases of male sexual abuse is similar to theirs. From January 1977 through February 1980, the committee reviewed 59 cases of suspected sexual abuse, 13.6% of which were boys with a mean age of 7.4 years (range, 3 months to 13 years). However, none of the perpetrators were strangers to the male victims and only 12.5% of the males demonstrated any injuries on physical examination. This contrasts with values of 56% and 50%, respectively, in their study. All of our males were first seen with the chief complaint of sexual abuse, as were theirs.

These figures imply that many cases of sexual abuse of boys are being missed by the medical community due to a low index of suspicion and the difficulty in detecting signs of sexual abuse during examination of the male child. In view of the fact that from 44% to 100% of the perpetrators are known by the victims, it would seem likely that many cases are not first seen with the chief complaint of sexual abuse. In our population, 67% of the female victims come with complaints unrelated to sexual abuse and, assuming comparability with the proportion of male cases that are not reported by the family, at least a third of all male cases, and probably more, remain undetected. We strongly believe that further studies of large

numbers of cases are needed to (1) determine those historical factors that might prompt the physician to perform a more thorough search for physical signs of sexual abuse, and (2) determine what subtle physical signs, if any, are associated with sexual abuse.

Ellerstein and Canavan are to be commended for focusing attention on this problem. A high index of suspicion and a careful examination for physical signs might pick up many cases that at present are being missed.

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Human Milk

Sir.—The results and conclusion of a recent report on cells and aqueous component of human milk by Gene L. France and associates require comment (JOURNAL 134:147-152, 1980).

It has been documented that human milk cells are functionally competent.[1,2] They are capable of ingestion and killing of microorganisms.[1,2] The aqueous component, on the other hand, is complementary to the cells in providing opsonins.[2] In addition, we have demonstrated that the milk cells are capable of reducing nitro blue tetrazolium.[3,4] Using the colostric leukocytes, this has been confirmed by France et al. The latter investigators, however, have reported a lack of chemotactic factor or factors in aqueous milk and a lack of chemotactic migration capacity by milk cells. We recently determined (using a modified Boyden's technique[3,4]) that milk cells obtained from 20 lactating women were capable of chemotactic migration in response to chemotactic factor or factors, and in the absence of chemotactic factors they exhibit random migration.[3,4] The aqueous component revealed chemotactic factor or factors that were partially heat labile.[4] The mean (±SD) chemotactic index (49 ± 19) of milk cells in response to activated serum was, however, less than (74 ± 25) that of blood neutrophils obtained from the same group of lactating women.[3,4] The results were similar with chemotactic factors obtained from *Escherichia coli*. The random migration of milk cells, in contrast, was more than that of blood neutrophils.[3,4]

It is difficult to account for the differences between our observations and theirs, especially in the absence of their actual results. They have used a different method[5] (agarose gel method) from ours,[3,4,6-8] but this is unlikely to be the only basis.

Their article does not include details of methodology such as day-to-day variation, variation of duplicate determinations, and confidence limits of the technique. Results obtained on the blood cells and milk cells have also been omitted. The control subjects (donors of blood cells) and the study subjects (milk donors) were also not well defined. The adverse effects of systemic infection,[9] diabetes, alcohol ingestion, and medications including aminoglycosides[8] on neutrophil chemotaxis are well known. Whether these factors were excluded in the study of the subjects was unstated. The neutrophils of the same lactating women, as measured in our study,[4] might have been a more appropriate control.

Based on our studies, we believe that milk cells are capable of chemotactic and random migration and that human milk has chemoattractive capacity. The latter may be a basic mechanism accounting for migration of blood cells in breast alveoli. In the absence of documentation, the conclusions of France et al appear unwarranted.

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1. Pittard WB III: Breast milk immunology: A frontier in infant nutrition. *Am J Dis Child* 133:83-87, 1979.
2. Robinson JE, Harvey BAM, Soothill JF: Phagocytosis and killing of bacteria and yeast by human milk cells after opsonisation in aqueous phase of milk. *Br Med J* 1:1443-1446, 1978.
3. Khan AJ, Rosenfeld W, Vadapalli M, et al: Chemotaxis and NBT reduction by breast milk leukocytes, abstracted. *Pediatr Res* 13:401, 1979.
4. Khan AJ, Rosenfeld W, Vadapalli M, et al: Chemotaxis and random migration of human milk cells. *J Pediatr* 96:879-882, 1980.
5. Nelson RD, Quie PG, Simmons RL: Chemotaxis under agarose: A new and simple method for measuring chemotaxis and spontaneous migration of human polymorphonuclear leukocytes and monocytes. *J Immunol* 115:1650-1654, 1975.
6. Khan AJ, Lee CK, Wolff JA, et al: Defects of neutrophil chemotaxis and random migration in thalassemia major. *Pediatrics* 60:349-351, 1977.
7. Khan F, Khan AJ, Papagaroufalis C, et al: Reversible defect of neutrophil chemotaxis and random migration in primary hyperparathyroidism. *J Clin Endocrinol Metab* 48:582-584, 1979.
8. Khan AJ, Evans HE, Glass L, et al: Abnormal neutrophil chemotaxis and random migration induced by aminoglycoside antibiotics: *J Lab Clin Med* 93:295-300, 1979.
9. Khan AJ, Evans HE, Glass L: Contradiction in neutrophil chemotaxis in bacterial infection. *J Pediatr* 84:444-445, 1974.

In Reply.—Dr Khan and his associates call attention to one aspect of neutrophil function, ie, chemotaxis, that we agree may be an important factor in host defense both for the mother in preventing breast abscesses and for the infant in providing neutrophils for antigen processing. Unfortunately, we have already imposed on the JOURNAL by submitting an unusually lengthy article and so omitted details of this particular assay. We chose to focus on data more specific to *Salmonella* infection.

Methods for chemotaxis under agarose were identical to those previously published[1] except that we quantitate the migrating cells with a micrometer disk (scale, 5 mm/100 units, type 9) eyepiece grid. After counting cells on the chemotactic side and control side of the neutrophil well, the chemotactic index is calculated using the following formula: chemotactic index (CI) = No. of cells on the chemotactic side/No. of cells on the control side. Our control values for peripheral blood neutrophils are 5.22 ± 1.89 (SD). Samples of colostrum and breast milk neutrophils from our 60 donors never demonstrated a CI greater than 1.3.

We have performed chemotactic assays in postpartum women and have found them to be no different from random control subjects; therefore, we found it unnecessary to draw blood from lactating women for these studies. Milk donors were healthy women not receiving medications and without systemic disease known to affect chemotaxis. We were careful in this selection since we were well acquainted with the literature referred to by Dr Khan.

Unfortunately, we are unable to comment on technical details that

might account for the findings of Khan et al since this work has only been published in abstract form.[2] We look forward to reading the forthcoming article.[3]

Suffice it to say that the two assays present quite different methodology, and this could certainly account for the discrepant results in question. There are many explanations, but we might offer this one. Increased neutrophil adherence in breast-milk leukocytes might decrease chemotaxis with the under agarose method (done on plastic plates) while not affecting measurement with the Boyden's chamber.

Previous investigators have demonstrated that the under agarose assay is more sensitive than the Boyden's one,[1] and we therefore chose the former methodology. We are also concerned with the high CI for the medium control reported by Khan et al.[2] Perhaps other readers of the JOURNAL have additional experience examining chemotaxis of breast-milk cells.

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1. Klein RB, Fischer TJ, Gard SE, et al: Decreased mononuclear and polymorphonuclear chemotaxis in human newborns, infants, and young children. *Pediatrics* 60:467-472, 1977.

2. Khan AJ, Rosenfeld W, Vadapalli M, et al: Chemotaxis and NBT reduction by breast milk leukocytes, abstracted. *Pediatr Res* 13:401, 1979.

3. Khan AJ, Rosenfeld W, Vadapalli M, et al: Chemotaxis and random migration of human milk cells. *J Pediatr* 96:879-882, 1980.

Neonatal Scabies

Sir.—The article by Burns et al, "Neonatal Scabies" (JOURNAL 133:1031-1034, 1979), is timely and achieves the stated goal of acquainting the reader with the observation that neonatal scabies has a different appearance than does scabies in older patients. However, some of their observations and statements are contrary to our experience.

The statement was made that the burrow of scabies is seldom seen in today's adult scabies and is rarer in infants and children. We have observed the burrow usually to be present in all ages, though often in altered form in infants. Examination of suspected scabietic patients must be meticulous. Adults may have as few as one or two burrows, which may be found in nondermatitic, nonpruritic areas. Burrows in children are often located on the palms, soles, and/or creases of the wrist. Casual inspection of the minute linear scale of a curved burrow may result in the incorrect conclusion that this represents merely the edge of an erosion or unroofed vesicle. In infants, the burrow is often altered by the pyodermic response. The clue is a linear arrangement of vesicles and/or pustules, which may be surmounted by an interrupted, fine linear scale. Identification of a burrow is very important, as this is the site of the mite, demonstration of which establishes the correct diagnosis. We do not abandon the search for the diagnostic burrow without a thorough and time-consuming examination.

Burns et al stated that the scabies mite survives only a few hours away from a human host. Thus, they did not recommend changing or laundering bedclothes or linen. Though survival time of the adult female mite has not been established, most estimates are in the one- to two-day range.[1,2] Though we agree that transmission by fomites is unusual, we believe that it is prudent to recommend at least minimal laundering and/or changing of bedclothes and linen. Perhaps the high initial treatment failure rate (40%) reported by Burns et al was from reinfestation through contaminated fomites.

We support the authors' decision not to use lindane (gamma benzene hexachloride) on neonates. However, they also stated that they could find no data to support the assumption that there is an increased likelihood of toxicity in neonates. Ginsberg et al[3] showed a borderline correlation between increasing serum lindane levels and decreasing age. Animal studies have shown significant brain levels from absorption of topically applied lindane.[4] Reports have described seizures and other CNS symptoms after use of lindane in all age groups,[5] but predominately in infants.[6]

The authors stated that antibiotic therapy was unnecessary since all evidence of secondary infection in patients treated with antiscabietic therapy alone cleared within a few days. There was no indication that bacterial cultures were taken from any patient, except the single patient who did receive antibiotics for a presumed staphylococcal dermatitis [sic]. Glomerulonephritis secondary to nephritogenic streptococci complicating a scabietic infestation has been reported.[7] If systemic antibiotic therapy is to be withheld in clinical pyodermas, then cultures should be taken to exclude these organisms.

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Nonproprietary Name and Trademarks of Drug

Lindane—*Gamene, Kwell, R & C.*

1. Gordon RM, Unsworth K: A review of scabies since 1939. *Br Med Bull* 3:209-215, 1945.

2. Mellanby K, Johnson DG, Bartley WC, et al: Experiments on the survival and behavior of the itch mite, *Sarcoptes scabiei* De B *var hominis*. *Bull Entomol Res* 33:267-271, 1942.

3. Ginsberg CM, Lowry W, Reisch JS: Absorption of lindane (gamma benzene hexachloride) in infants and children. *J Pediatr* 91:998-1000, 1977.

4. Solomon LM, West DP, Fitzloff JF, et al: Gamma benzene hexachloride in guinea-pig brain after topical application. *J Invest Dermatol* 68:310-312, 1977.

5. Lee B, Groth P: Scabies: Transcutaneous poisoning during treatment. *Pediatrics* 59:643, 1977.

6. Pramanik AK, Hansen RC: Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. *Arch Dermatol* 115:1224-1225, 1979.

7. Lasch EE, Frankel V, Vardy PA, et al: Epidemic glomerulonephritis in Israel. *J Infect Dis* 124:141-147, 1971.

In Reply.—Drs Dolezal and Plamondon bring out several aspects of scabies that were mentioned only briefly in our publication due to the limited scope of the article. A unique feature of the current pandemic is that classic scabies is seldom seen and less typical varieties such as minimal scabies in the unsoiled patient are predominating.[1-3] Only 7% of more than 1,000 patients studied in Goa, India from 1969 to 1970 were found to have burrows.[4] In the study of Hejazi and Mehregan,[5] burrows were absent in over 70% of patients. No burrows were present in any of the neonates described in our study (nor in 11 additional neonates examined since). In only four of the contacts of these 16 infants was there even a suggestion of a burrow.

Whether one states that mite survival time is a few hours or one to two days is a matter of semantics rather than a difference of opinion. Under

ideal conditions, mite survival away from the human host has been observed for up to 96 hours.[6] (My own observations noted a disappointing seven hours in one case and 11 hours in a hardier female.)

The role of fomite transmission was clearly delineated by Mellanby's classic experiments with human volunteers.[7] After six months, he was able to transmit scabies via fomites in only two persons who exchanged underclothes directly with infected subjects. When underclothes were allowed to sit (unlaundered) for two or more days, no transmission occurred. Blankets, bedclothes, and outer garments were shown to have no role in transmission of the mite. In like manner, meticulous studies conducted during World War II by the Medical Research Council of the United Kingdom showed that it is exceedingly difficult to transmit scabies by any fomite.[8] Many physicians still insist on strict laundering and sterilization of fomites, but this simply is not necessary. At most, a simple change of clothing (specifically underclothes) after therapy is all that is needed.

I was pleased to note that Drs Dolezal and Plamondon supported our position against the use of lindane in very young children. Unfortunately, when our literature search on lindane was conducted, their references had not yet been published.

Cultures were taken from all of our infant patients. From two infants, coagulase-positive staphylococci were isolated, and *Staphylococcus epidermidis* was recovered from another. The relationship between acute glomerulonephritis (AGN) and nephritogenic group B streptococci is well documented. Though the relationship between AGN and scabies is less well defined, the potential is certainly there. We still, however, reserve the use of antibiotics for those cases where superinfection is severe and nephritogenic strains are isolated. The injudicious use of antibiotics in other patients is not warranted.

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1. Juranek D, Schultz NG: Epidemiologic investigations of scabies in the United States, in Orkin M, Maibach H, Parish L, et al (eds): *Scabies and Pediculosis*. Philadelphia, JB Lippincott Co, 1977, pp 27-31.
2. Orkin M: Today's scabies. *JAMA* 233:882-885, 1975.
3. Orkin M, Maiback HI: Pediatric dermatology: Scabies in children. *Pediatr Clin North Am* 25:371-386, 1978.
4. Sehgal VN, Rao MA, Rege MB, et al: Scabies: A study of incidence and a treatment method. *Int J Dermatol* 11:106-111, 1972.
5. Hejazi N, Mehregan AH: Scabies: Histological study of inflammatory lesions. *Arch Dermatol* 111:37-39, 1975.
6. Heileson B: Studies on *acarus scabiei* and scabies. *Acta Derm Venereol (Suppl)* 26:1-370, 1946.
7. Mellanby K: The transmission of scabies. *Br Med J* 2:405-408, 1941.
8. Moschella S (ed): *Dermatology*. Philadelphia, WB Saunders Co, vol 2, 1975, pp 1487-1552.

Psychological Factors in Diabetes Mellitus

In their extensive and excellent review in the JOURNAL on the psychological factors in diabetes mellitus (133:1061-1066, 1979), Greydanus and Hofmann missed three books and proceedings of recent meetings[1-3] devoted to the psychological aspects of diabetes in children, in which investigations from various professions from all over the world were brought together.

For the past 20 years we have been convinced that once diagnosed, diabetes becomes a somatopsychic disease in juveniles and a source of anxiety for the parents.[4] We have seen that without the achievement of emotional stability in the family, the diabetes in the child cannot be controlled.[5] Our experience has led us to include psychologists and social workers in the team treating diabetic children and adolescents.[6]

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1. Laron Z (ed): *Habilitation and Rehabilitation of Juvenile Diabetics*. Leiden, the Netherlands, H. E. Stenfert Kroese N. V., Leiden, 1970.
2. Laron Z, Karp M (eds): *Diabetes in Juveniles: Medical and Rehabilitation Aspects*, ed 2. Basel, Switzerland, S Karger AG, 1977.
3. Laron Z (ed): *Psychological Aspects of Balance of Diabetes in Juveniles*. Basel, Switzerland, S Karger AG, 1977.
4. Laron Z: Treatment of diabetes in children: Revisited. *Pediatr Ann* 3:63-77, 1974.
5. Laron Z: Opening address, in Laron Z (ed): *Psychological Aspects of Balance of Diabetes in Juveniles*. Basel, Switzerland, S Karger AG, 1977, p *X*.
6. Laron Z, Galatzer A, Amir S, et al: A multidisciplinary, comprehensive, ambulatory treatment scheme for diabetes mellitus in children. *Diabetes Care* 2:342-348, 1979.

In Reply.—I thank Professor Laron for his interest and remarks. It was not possible to include all pertinent references and books in the compilation of our review. Thus, with some exception, attention was mainly directed to articles in peer-review journals. I welcome the inclusion of the cited symposiums.

I fully agree with his comments regarding the importance of family stability in the life of juvenile and adolescent diabetics. The review sought to present an overview of psychological or emotional factors in stabilizing teenage diabetics. As indicated, there are many factors involved, each one of which needs more investigation. Many approaches are used in seeking to prevent or manage "poor" teenage diabetic control. I emphasize a primary physician-adolescent patient relationship in which the clinician seeks to invest as much self-care as possible.[1] The family is encouraged to contribute to this therapeutic plan. Physician, adolescent, and parents form a team to aid with successful management. Psychiatric or psychological care is necessary if brittleness develops on an emotional basis.

The use of psychologists or social workers as part of a team dealing with the patient may be useful for many. The Adolescent Medical Clinic at the University of Rochester (NY) Medical Center emphasizes an approach utilizing a pediatric or adolescent medicine specialist to care for the diabetic patient, with psychiatric or psychological evaluation and consultation as needed. The family remains an important part of the health care plan. Some note that direct family therapy is important for labile diabetics.[2] I have found this useful in some but not all diabetics. It is up to the clinician to decide which therapeutic approach fits a particular teenage diabetic and his/her family. More research is needed in this area.

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1. Greydanus DE, Hofmann AD: A perspective on the brittle teenage diabetic. *J Fam Pract* 9:1007-1012, 1979.
2. Minuchin S, Rosman BL, Baker L: *Psychosomatic Families: Anorexia Nervosa in Context*. Cambridge, Mass, Harvard University Press, 1978, pp 23-50.

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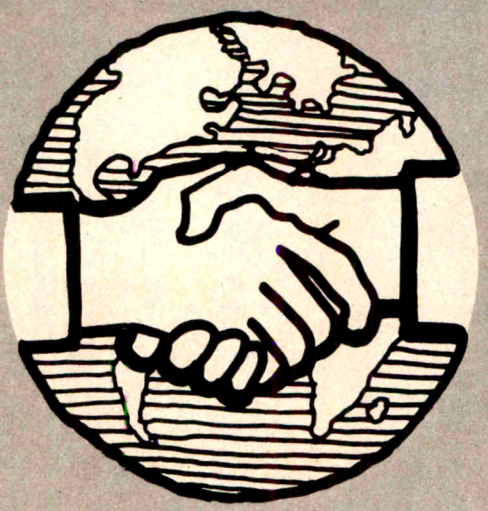

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Books

Project Head Start: A Legacy of the War on Poverty, edited by Edward Zigler and Jeanette Valentine, 610 pp, $22.50, New York, Macmillan Publishing Co Inc, 1979.

In recent years, it has seemed that we Americans are so given to self-flagellation that we cannot stand up and applaud anything. There were some victories scored in Lyndon Johnson's war on poverty, but none greater than Project Head Start. As the book jacket states:

> When Project Head Start was organized in 1965, its goals mirrored the hopes of millions of impoverished Americans. Initially funded as a short-term effort, Head Start has become, after more than a decade of operation and a cost of approximately $2 billion, the most ambitious educational, social and health program for young children and their families in United States history.

This book, edited by Edward Zigler and Jeanette Valentine, examines the experience through the eyes of 35 authors from many disciplines. Most of them had a hand in Head Start.

As with most multiauthored volumes, there is much repetition. Tight editing is not in evidence. A few chapters were published previously and add to the bulk. Then there is too much "old-boy" reminiscing ("where I was when I got the call from Sarge Shriver") of interest only to the Head Start "in-group." With these few insignificant caveats, I recommend the book as required reading for anyone interested in early childhood evaluation.

My three favorite chapters are the ones by Catherine Ross on the historical roots of Head Start, by James Robinson and Willa Barrie Choper on parents' perspective of Head Start, and by Francis Palmer and Lucille Andersen reviewing the numerous longitudinal studies on long-term gains from early intervention. An interesting historical note is provided on the premature release of the so-called Westinghouse report in 1969, purporting to show the program's failure. Richard Orton says that the resultant publicity ("the blackest day in the history of the program") was directly orchestrated by the Nixon White House in an effort to kill Head Start. The blackest day as far as pediatricians are concerned is when the American Academy of Pediatrics lost the consultation contract to the self-same Westinghouse Corporation. This issue is politely glossed over in the book, with some pablum about "administrative difficulties" within the Academy. Another item not discussed is the virtual exclusion of handicapped children from Head Start.

What is continually stressed is that Head Start should not be viewed as simply an educational experience. I agree that "the innovative idea . . . is that effective intervention in the lives of children can only be accomplished through involving parents and the community in the intervention effort." In these days of militant teachers unions, and legal wrangles over busing, parents are less involved in their children's public school education.

For middle and upper class America, 4 years has become the accepted age to start school. Where does this leave the children of the poor who are most in need of an enriched environment? Head Start is the only hope and this book tells why.

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Pediatric Nephrology, by Charles E. Hollerman, 501 pp, $16.50, Garden City, NY, Medical Examination Publishing Co Inc, 1979.

The intent of this book, as declared in the preface, is to provide information about the diagnosis and treatment of renal disease for physicians providing primary care to neonates, children, and adolescents. Accordingly, this text differs from those like *Pediatric Nephrology* by Rubin and Barratt, *Pediatric Kidney Disease* by Edelmann, or *Pediatric Nephrology* by Royer et al that are intended primarily for nephrologists. Dr Hollerman's text is akin to *Renal Disease in Childhood* by James, which is also intended for primary care physicians. It is also comparable to the James' text in that it is single authored and thus reflects opinions and experiences of a single physician.

The book is arranged in 16 chapters and covers the entire spectrum of renal disorders that affect neonates, children, and adolescents. It is a paperback book with offset printing that is convenient to carry and easy to read. Topics covered include glomerular and tubular disorders, genetic diseases, hypertension, renal disorders of the neonate, acute and chronic renal failure, and a chapter on dialysis and transplantation. All chapters contain current information and the list of references at the end of each chapter reflects careful selection of the best reviews and current papers on the subject of the chapter. At the end of each chapter is a series of five multiple-choice questions whose answers are given in a short essay.

As the author states, his opinions prevail throughout the text, which results in the shortcomings of this book. In a brief text like this there is little room for a discussion of the pathophysiology of glomerular or tubular disorders, and the pathophysiologic mechanisms of acute renal failure are discussed by merely listing the prevailing theories. The major arguments on either side of certain controversial topics are not covered, eg, the use of anticoagulant therapy of the hemolytic uremic syndrome, the use of corticosteroids for membranous nephropathy, high-dose intravenous methylprednisolone treatment of rapidly progressive glomerulonephritis or other crescentric glomerulonephritides. Some nephrologist might not dismiss the value of a low-salt diet in edematous nephrotic children or might believe that a 30-hour water deprivation test is needed to evaluate maximal urinary concentration capacity. In the discussion of antihypertensive agents, neither saralasin or captopril, which act to block the renin-angiotensin system, are discussed. This would be helpful since these agents act by an entirely separate mechanism than those listed. There is no discussion of plasmapheresis as a mode of treatment of glomerulonephritis or of lactic dehydrogenase isozyme pattern for detecting the location of urinary tract infections. Some obscure topics are covered, such as amyloidosis associated with familial Mediterranean fever and Ehlers-Danlos syndrome, and yet there is no

indication that the former can be treated with colchicine or that the latter is associated with renal tubular acidosis. Perhaps the most confusing aspect was the inclusion of the site of action and dosage of various diuretics in a chapter on the assessment of renal symptoms.

Despite these minor shortcomings, this is an excellent text. The references are particularly useful and I plan to use them extensively over the next few years as they are both comprehensive and current. Each chapter contains some very good tables that in many instances have been compiled by the author from several sources in order to construct tables of real use to the clinician. The table on renal growth during childhood is most impressive. There are clear descriptions of all disease entities and the chapter on renal dysplasia, hypoplasia, and cystic disease is very clear. The index is complete.

The relatively low price of this book and its clear, concise presentation make it a valuable text for primary physicians and residents treating children with renal disorders. I intend to recommend it to our residents.

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Textbook of Child Neurology, ed 2, by John H. Menkes, 695 pp, Philadelphia, Lea & Febiger, 1980.

The second edition of Menkes' *Textbook of Child Neurology* remains the most generally useful in the field. It is comprehensive, yet not oversized, the second edition representing the addition of about 100 pages. Menkes cites a number of developments, particularly the computerized tomographic (CT) scan, to warrant the second edition, but in fact CT scan representation of neurologic disease is not extensively presented. For example, the section on "Congenital Anomalies" would profit by more in vivo CT illustrations of the gross malformations described, and a number of other sections would profit as well. The book retains the considerable advantage of essentially single authorship, which gives balance and not too much bias to the presentation. At the same time, the contribution by colleagues is excellent, particularly Dr Gabriel's discussion of malformations of the CNS and Dr Kinsbourne's chapter on "Disorders of Mental Development." As might be expected, the section on metabolic disease is strong, as is the chapter on "Paroxysmal Disorders," both areas of particular interest of the author, especially metabolic disease where Dr Menkes has made substantial contributions and displays a strong grasp of the biochemical aspects. One wonders, however, why metachromatic leukodystrophy and Krabbe's disease still find their home in the chapter on heredodegenerative disorders rather than in the more appropriate section on metabolic disease, inasmuch as the basic defects are as well understood as most disorders contained in the metabolic chapter. I also wonder why he retains the chapter heading "Perinatal Trauma" when the subject covered, and certainly the problem in 1980, is better described as "hazards of birth in the perinatal period." Also, a somewhat more extended and in-depth presentation of the modern issues related to intraventricular hemorrhage in the premature would be useful.

However, the real judgment on this book is not based on a number of small points but is to state again unequivocally that this is the most comprehensive yet concise presentation of child neurology for a readership that includes pediatricians, generalists, and people who are in training for pediatrics, neurology, or child neurology. It is an excellent book, better than the first edition in a number of ways, and will surely warrant a third edition in a few years.

CHARLES F. BARLOW, MD
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Muscle Disorders in Childhood, by Victor Dubowitz, 282 pp, Philadelphia, WB Saunders Co, 1978.

This monograph is 16th in the series *Major Problems in Clinical Pediatrics.* It lives up to the excellent reputation of the series by presenting the personal approach to muscle disorders of Victor Dubowitz, MD, who is internationally known and respected for his expertise in this area. The presentation is systematic, well written, and profusely illustrated, as well as authoritative. The confusing nomenclature of the ultrastructurally designated congenital myopathies is well handled, though one comes away with the notion that separation of this group of nonprogressive or very slowly progressive disorders is artificial at this level, and perhaps a fresh start with less emphasis on ultrastructure is the way of the future.

In addition to a workman-like presentation of the expected subjects of dystrophy, disorder of the lower motor neurons, myasthenia gravis, and the inflammatory myopathies, the author deals effectively with the somewhat newer and therapeutically important issues, such as carnitine myopathy and malignant hyperpyrexia. The expected chapter on the "floppy infant syndrome" is well covered, as is the section that deals with arthrogryposis and congenital contractures, which correctly presents this latter group as a symptomatic expression of prenatal neurologic disorder of movement in utero. With regard to the floppy infant, I suspect that the disappearance of this favorite subject of pediatric neurologists will coincide with a true coming of age of the field, vis-à-vis adult neurology. The adult neurologists have gone several generations beyond the floppy adult, but they still have their "stiff man." Probably the weakest chapter in the book is the one that deals with disorders of movement.

All in all, it is an excellent presentation of an important aspect of pediatrics and can be fully recommended as authoritative and up to date.

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Emergency Radiology of the Acutely Ill or Injured Child, by Leonard E. Swischuk, 496 pp, with illus, $45, Baltimore, Williams & Wilkins Co, 1979.

This book of almost 500 pages is devoted to that aspect of emergency pediatrics for which diagnoses are made with the aid of radiological examinations. The author aims to outline (1) general approaches to diagnostic problems, (2) helpful rules of thumb, and (3) specific diagnostic signs. Sometimes he delves convincingly into pathophysiologic-roentgenographic correlations.

The roentgenographic contribution is emphasized with 564 figures of generally excellent quality, which contain approximately 1,088 roentgenograms. Only a few examples of other radiological diagnostic methods are included: nine computerized tomograms, three sonograms, and five radionuclide scans. Illustrative line drawings are effectively used in 25 instances to

help clarify diagnostic features. One graph and three tables also complement the text. Pertinent, recent, and mainly US references are conveniently listed after each subsection, which allows for easier retrieval.

Normal variations, where appropriate, are distinguished from abnormal findings, especially in the skull, vertebral column, and limbs.

A few controversial concepts, such as those concerning intussusception and methods of reduction are offered, but mainly a conventional viewpoint is espoused.

The book is not comprehensive, and the statement "... a complete discussion is beyond the scope of this book..." is appropriately used in several instances.

Overall, the aims of the author are more than adequately accomplished, and the book is a useful addition to the radiology literature of pediatrics. It contributes substantial information on the radiologic aspects of the acutely ill or injured child. It should benefit pediatricians, general radiologists, residents, and medical students.

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Fetal and Maternal Medicine, by E. J. Quilligan and Norman Kretchmer, 681 pp, $40, Somerset, NJ, John Wiley & Sons Inc, 1980.

The true scope of perinatal medicine, the study of human creation, is vast. No one book can encompass the psychological, physiological, and pathophysiological processes involved from conception through a successful neonatal period, but Drs Quilligan and Kretchmer have done for perinatal medicine what Mahler and Handel did for a different Creation: captured its spirit. They did not attempt to write a bible.

In *Fetal and Maternal Medicine*, Drs Quilligan and Kretchmer have gathered together edited contributions from noted authorities and produced a valuable resource book for nurses and physicians interested in perinatal medicine. The content of the book is divided into three sections: basic concepts, systemic problems, and specific diseases. The assignments are sometimes quite arbitrary: for example, the inclusion of "Pulmonary Surfactant and the Respiratory Distress Syndrome" under basic concepts. Nevertheless, the editors were able to maintain a clear focus on the mother, her problems as they affect her and the fetus, and the period immediately after birth. The initial chapter on statistics on perinatal morbidity and mortality lays a solid foundation for consideration of the subsequent subjects. A few of the chapters are somewhat skimpy ("The Effects of Drugs on Uterine Contractility," "Fetal Distress"); most are very good; and a few ("Human Perinatal Endocrinology," "Immunology") are outstanding summaries of complex areas. The only chapter that seems out of place in this constellation is the final one, which considers the low birth weight infant and its bilirubin problems. In general, the writing is clear and concise, and material is presented in a well-organized and easily readable format. Although perhaps not covered systematically, almost all important subjects relevant to maternal-fetal medicine are covered. One notable exception is the role of intrauterine physical environment on dysmorphogenesis.

In the introduction, the editors stated their desire to have each subject discussed jointly by a pediatrician and an obstetrician. Although only three of the 27 chapters are the product of such a collaboration, the partnership of a pediatrician and an obstetrician in editing the book is reflected throughout and is symbolic of today's partnership in perinatal medicine. This book would serve equally well as a reference source for pediatricians or obstetricians, a high compliment for books in this area. I commend the editors and recommend their book to professionals in need of an up-to-date, reasonably comprehensive, lively resource work in perinatal medicine.

DONALD SHAPIRO, MD
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Adolescent Medicine in Primary Care, by Walter R. Anyan, Jr, 387 pp, New York, John Wiley & Sons Inc, 1978.

Dr Anyan wrote this book primarily for health care practitioners whose disciplines are pediatrics, internal medicine, and family medicine. The intent of the book is to focus on specific aspects of adolescent health care, development processes, and disorders that are specific to the adolescent. It is not intended to be an encyclopedia for all medical disorders that occur in the adolescent but rather those that are most peculiar to or influenced by the process of adolescence.

The book is divided into three general sections. The first is on organization and conduct of adolescent primary care. This general approach to history taking, physical examination, and the data base is a more than adequate guide to the different approaches to and the different needs of the adolescent, as differentiated from the child or adult.

The second section focuses on the physiologic basis for adolescent care, specifically sexual maturation and the pubertal process. This section is relatively long and in some parts it is more detailed than is necessary for clinical care of the adolescent. Specifically, the section on "Changes in Hypothalamic and Anterior Pituitary Function" is much too complex for the physician involved in giving clinical care to the teenager. The same holds true for the discussion on changes in body composition. Though the concepts are important, the detailed presentation is probably not necessary for the intended audience of this book.

In the third section, the choice of topics for clinical problems in adolescence is appropriate though limited. For example, the major clinical conditions associated with the sexually active adolescent are adequately explored. Exceptions are the difficult problems associated with the diagnosis and treatment of pelvic inflammatory disease, which were not adequately emphasized. In addition, the section on teenage pregnancy does not reflect the major issues associated with this difficult problem nor the kinds of approaches necessary to try to resolve it, either on an individual basis or as a national problem.

The major difficulty with this book is the unevenness of the treatment of subjects throughout. That is, some subjects are discussed in a much too detailed fashion, while others are treated too superficially. Generally, the writing is literate and the book is easy to read. This book would be valuable for house staff and practicing physicians in pediatrics, internal medicine, and family practice.

FELIX P. HEALD, MD
Division of Adolescent Medicine
Department of Pediatrics
University of Maryland School of Medicine
Baltimore, MD 21201

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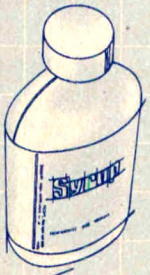

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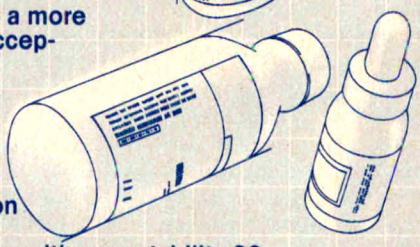

"...expectoration and decongestion are my prime objectives—along with acceptability."

"Pseudoephedrine is a stimulant. I don't think it's a good idea in infants under two years."

"[When treating very young children,] you don't want to suppress the cough."

"I do not prescribe codeine for small children. I prefer dextromethorphan."

"I think the taste factor is also important...so do the mothers!"

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FOR INFANTS & CHILDREN
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FOR INFANTS & CHILDI
No codeine or other narcotic atives.

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No subtherapeutic formulations, treatment failure or necessitating inc dosage.

INTRODUCIN

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TIONAL SYMPTOMATIC THERAPY.

STEP 3. STEP 4.

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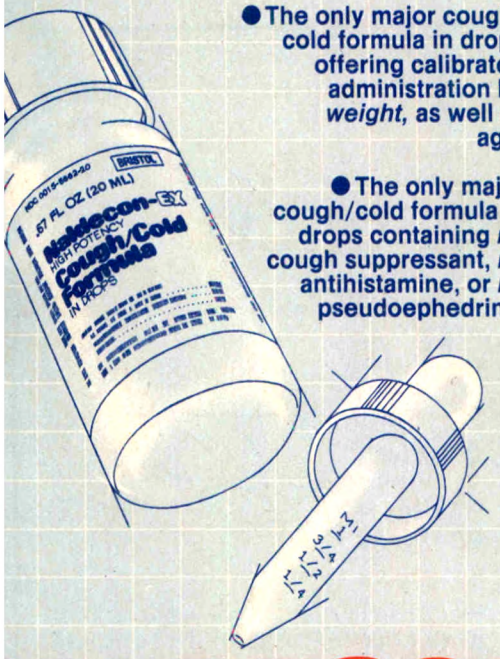

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Alcohol 5%

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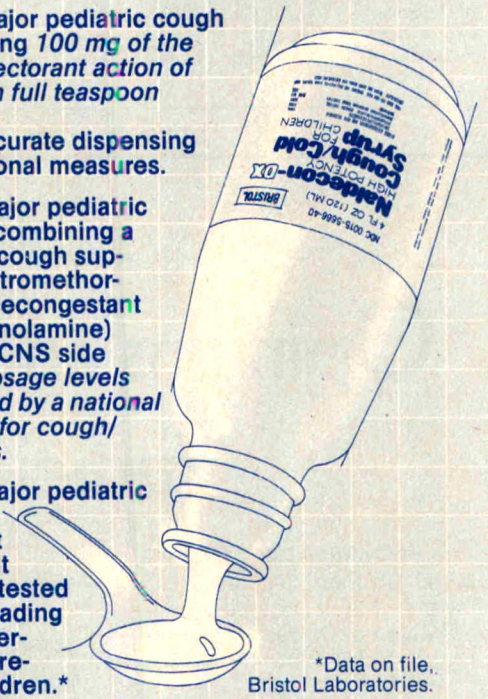

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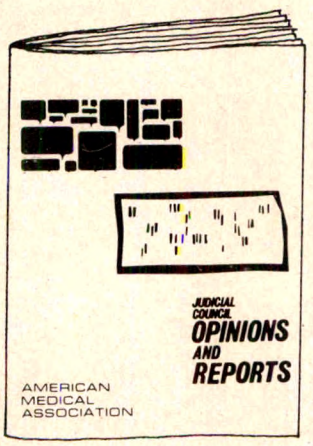

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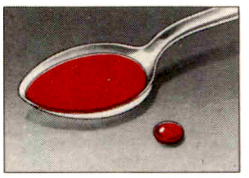

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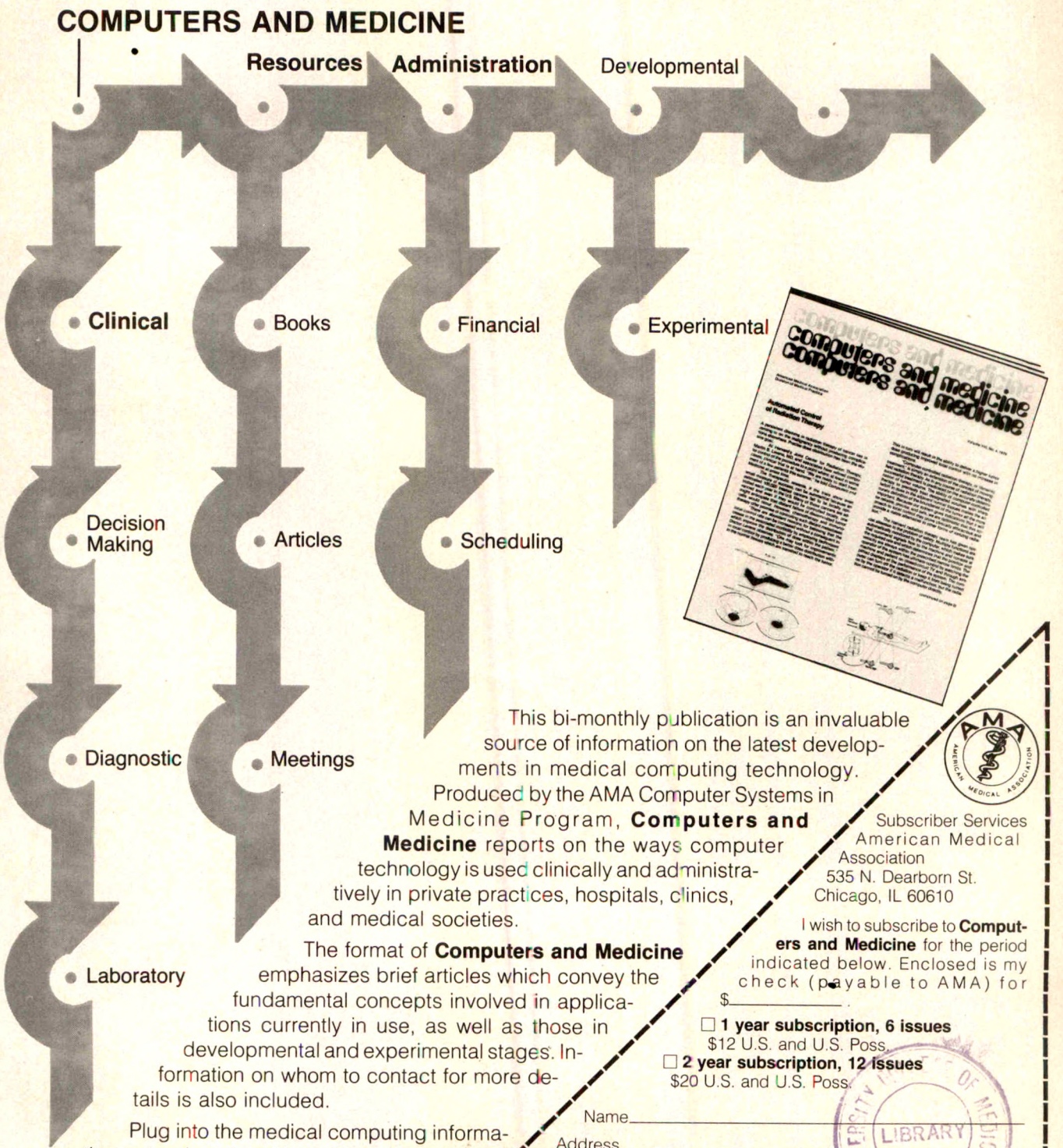

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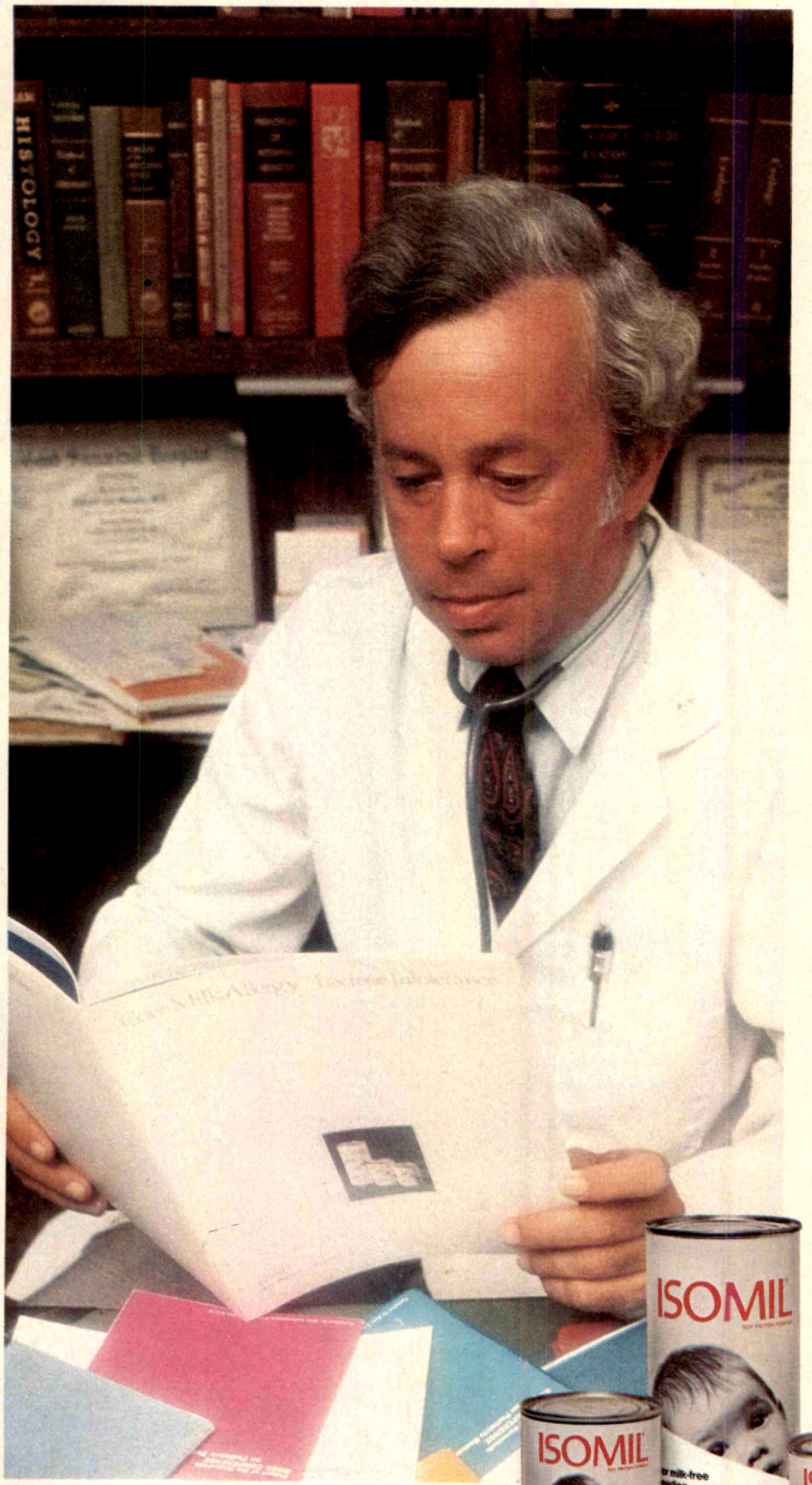

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3. Leake RD, Schroeder KC, Benton DA, et al: Soy-based formula in the treatment of infantile diarrhea. *Am J Dis Child* 127:374, 1974.
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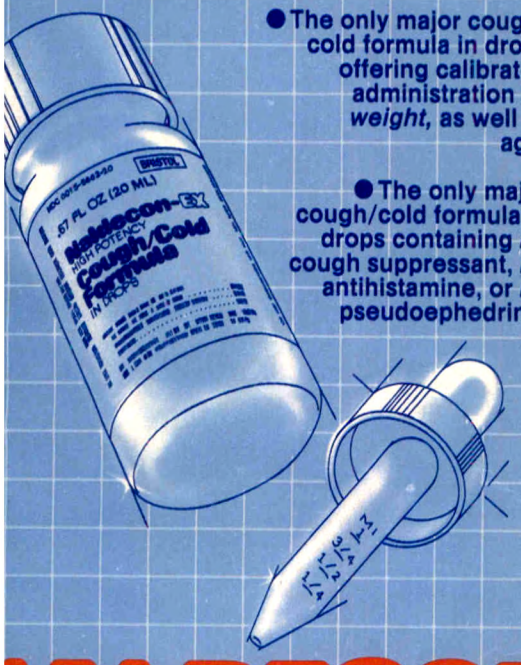

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Evaluation of Neonatal Periventricular-Intraventricular Hemorrhage

A Major Advance

Periventricular-intraventricular hemorrhage is the most common and serious variety of neonatal intracranial hemorrhage.[1] The other major types of hemorrhage, ie, subdural hemorrhage, primary subarachnoid hemorrhage, and intracerebellar hemorrhage, are either very uncommon or not of major clinical importance. The enormous importance of periventricular-intraventricular hemorrhage is linked to the evolution of neonatal intensive care and, as a consequence, the dramatic improvements in survival rates for small premature infants. Because periventricular-intraventricular hemorrhage is characteristic of such infants, the occurrence of the lesion has reached nearly epidemic proportions in modern neonatal intensive care facilities.

The adaptation of the computerized tomographic (CT) scan to the evaluation of the small premature infant in the mid-1970s led to the recognition of the remarkably high incidence of the lesion. Thus, in two large studies in which small premature infants were subjected to CT scan routinely in the first week of life, the incidence of periventricular-intraventricular hemorrhage was found to be 40% to 45%.[2,3]

In the following discussion, a brief review of the neuropathology, pathogenesis, clinical features, evaluation, outcome, and management of neonatal periventricular-intraventricular hemorrhage will be presented. These issues are discussed in considerable detail elsewhere.[1] In this article, particular emphasis will be placed on the evaluation of periventricular-intraventricular hemorrhage and, particularly, the major advance in recognition of the lesion made possible by the use of real-time ultrasound scanning (see article by Allan et al p 1028 in this issue).

NEUROPATHOLOGY

The neuropathological appearance of periventricular-intraventricular hemorrhage is distinctive and dramatic. The essential lesion is a hemorrhage into the subependymal germinal matrix. This critical region, the source of cerebral glia in perinatal brain (and of neurons earlier in gestation), is richly vascularized. The hemorrhage emanates from capillaries within the matrix.[4]

The site of the hemorrhage within the matrix bears a distinct relation to gestational age.[5] In the majority of cases that are recognized during life, ie, infants of approximately 28 to 32 weeks' gestation, the lesion occurs principally at the level of the head of the caudate nucleus. In infants less than 28 weeks of gestation, the site of the lesion is usually over the body of the nucleus caudatus, and in mature infants, the choroid plexus.

Approximately 80% of the cases of matrix hemorrhage rupture into the ventricular system. Blood spreads through the ventricles into the basilar cisterns in the posterior fossa. An obliterative arachnoiditis results and causes the impairment in CSF flow that promotes hydrocephalus.

PATHOGENESIS

Major insight into the pathogenesis of periventricular-intraventricular hemorrhage has been gained in the past several years. Pathogenetic formulations should explain the strong association of the lesion with prematurity and with the hypoxic events so frequently observed in premature infants, as well as the characteristic periventricular locus of the lesion.

The association of the lesion with prematurity relates to four major factors. First, the subependymal germinal matrix, which provides poor support for the small vessels coursing through it, does not dissipate until term in the human brain. Second, a disproportionate amount of cerebral blood flow appears to be diverted to the periventricular region because of the particularly exuberant vascular supply to the matrix. Third, the integrity of the periventricular capillary bed appears to be tenuous. Fourth, vascular autoregulation, the process by which cerebral arterioles constrict or dilate to maintain constant cerebral blood flow despite changes in perfusion pressure, is impaired in the human newborn.[6]

The occurrence of the lesion in certain infants with serious hypoxic events, eg, asphyxia, relates to four major factors. First, vascular autoregulation is more severely impaired under such circumstances, thus exposing the periventricular capillary bed to bursts of pressure-flow that might cause rupture. Second, cerebral blood

flow initially is increased with events such as asphyxia. Third, venous pressure may be increased, secondary to myocardial failure. Fourth, a degree of injury to the metabolically active capillary endothelial cells may occur with hypoxic insults.

The characteristic periventricular locus of the lesion relates to five major factors. The first three, discussed above, have to do with the facts that the periventricular region is the site of the germinal matrix, of a relatively prominent arterial supply, and of a capillary bed with apparently tenuous integrity. In addition, certain anatomic peculiarities of the deep venous drainage in the periventricular region[7] and a relatively large amount of fibrinolytic activity in this region[8] also probably have pathogenetic importance.

CLINICAL FEATURES

The clinical features of this lesion can be categorized into two basic syndromes. The first is a catastrophic deterioration that usually occurs in infants with larger hemorrhages and results in a serious outcome. The second is a more saltatory or stuttering deterioration that usually occurs in infants with smaller hemorrhages and has a less serious outcome. The features of the second syndrome may be so subtle that they are readily overlooked. Indeed, in one careful study only approximately 50% of the cases of periventricular-intraventricular hemorrhage were correctly predicted to have the lesion on the basis of clinical criteria.[9]

EVALUATION

Recognition of neonatal periventricular-intraventricular hemorrhage requires three essential steps. The first is identification of the clinical setting (essentially every premature infant in a neonatal intensive care unit). The second is recognition of the characteristic CSF profile, ie, initially many RBCs and an elevated protein content, followed shortly by xanthochromia, and a depressed glucose content. In a study of 76 consecutive infants (< 2,000 g at birth) who had a CT scan following the finding of the characteristic CSF profile of intraventricular hemorrhage, we found that only six (8%) had a normal scan, 22 (29%) had primary subarachnoid hemorrhage only, and 48 (63%) had clearly discernible periventricular-intraventricular hemorrhage.[10] Thus, in the presence of a CSF profile that suggests hemorrhage, the third step in the diagnostic sequence, ie, imaging of the intracranial cavity by CT or sonar scan, is indicated.

A CT scan is a highly effective means of establishing the diagnosis of periventricular-intraventricular hemorrhage and of demonstrating the site and extent of the lesion. In addition, the size of the ventricles, pattern of ventricular dilation, and presence of major white matter lesions (eg, periventricular leukomalacia) may also be defined. Despite the value of the CT scan, it must be recognized that the procedure is not without hazard to the small premature infant. Maintenance of ventilation, circulation, and temperature are difficult problems during transport and during the procedure itself. Moreover, although with modern instruments the radiation dose to the brain and eyes is comparable with that of conventional skull roentgenograms, the long-term effects of multiple scans over short time periods remain unknown.

Ultrasonic scanning now appears to be a safe, effective alternative to the CT scan. Use of the real-time, mechanical sector scanner, placed over the anterior fontanel and oriented in the coronal plane, provides excellent resolution of periventricular as well as intraventricular hemorrhage. The extent of intraventricular blood and severity of ventricular dilation is demonstrated by use of the sector scanner oriented in the sagittal plane. Use of a linear-array transducer over the side of the cranium provides a horizontal projection (comparable to the usual CT scan), which is particularly useful to quantitate degree of ventricular dilation (though is less effective in our hands in resolution of periventricular-intraventricular hemorrhage).

The ultrasonic technique is particularly attractive because portable instruments can be used; thus, the infant need not be transported or otherwise disturbed. Several studies can be performed over relatively short time periods, presumably without harm from the pulsed ultrasound. Such studies have obvious and major value for management, and may prove enormously useful for delineation of the pathogenesis of the hemorrhage. It is in the latter area that ultrasound may provide its greatest contribution, because the major goal of the management of periventricular-intraventricular hemorrhage is prevention. The latter goal can be attained only by identification of those pathogenetic factors that can be modified.

OUTCOME AND MANAGEMENT

Outcome of periventricular-intraventricular hemorrhage is related to six major factors. These include the following: (1) the neurological injury caused by preceding hypoxic ischemic insult or insults; (2) the degree of intracranial hypertension and resulting impaired cerebral perfusion that accompany the larger lesions; (3) destruction of periventricular white matter from intracerebral extension of blood; (4) destruction of germinal matrix (and its glial precursors) by the hemorrhage; (5) focal brain ischemia secondary to vasospasm; and (6) posthemorrhagic hydrocephalus. Initial data indicate a close relation between severity of the hemorrhage and neurological outcome. Infants with lesions of slight or moderate severity are normal on relatively short-term follow-up in the majority of cases. Infants with severe hemorrhages are normal on relatively short-term follow-up in only a small minority of cases.

Management must begin with the ethical decision of whether or not to treat. This critical issue requires careful consideration of clinical and brain imaging data. Cerebral perfusion must be maintained, and this will require maintenance of adequate blood pressure and, if necessary, lowering of increased intracranial pressure. Cerebral overperfusion must be prevented, especially because of the impaired vascular autoregulation. Thus, arterial hypertension, hypercapnia, hypoxemia, acidemia, and rapid infusion of hyperosmolar solutions or

colloid should be avoided. Diligent support of temperature, ventilation, and metabolic status is critical. Moreover, serial assessment of ventricular size by sonar or CT scans is necessary to detect ventricular dilation, which appears before clinical signs.[11] Therapy for posthemorrhagic ventricular dilation is reviewed in detail elsewhere.[1]

CONCLUSION

In the past five years there have been several major advances in the study of neonatal periventricular-intraventricular hemorrhage, eg, the advent of the CT scan, the recognition of the importance of the distribution and the regulation of cerebral blood flow in the newborn, and, now, the use of real-time ultrasonic scanning. The value of the latter in recognition of periventricular-intraventricular hemorrhage is demonstrated superbly by the study of Allan et al, found elsewhere in this issue. This role for ultrasonic scanning should prove to be very important. However, perhaps still greater value will accrue from application of this technique to research directed toward understanding of those factors that lead to this extremely frequent and serious lesion. At least some of these factors may be modifiable, and such modification could result in prevention of many cases of periventricular-intraventricular hemorrhage. Should this occur, ultrasonic imaging of the intracranial cavity will prove to be one of the most important advances ever made in the study of this hemorrhage.

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References

1. Volpe JJ: *Neurology of the Newborn*. Philadelphia, WB Saunders Co, to be published.
2. Papile L-A, Burstein J, Burstein R, et al: Incidence and evaluation of subependymal hemorrhage: A study of infants with birth weights less than 1,500 grams. *J Pediatr* 92:529-534, 1978.
3. Ahmann PA, Lazzara A, Dykes FD, et al: Intraventricular hemorrhage in the high-risk preterm infant: Incidence and outcome. *Ann Neurol* 7:118-125, 1980.
4. Hambleton G, Wigglesworth JS: Origin of intraventricular hemorrhage in the preterm infant. *Arch Dis Child* 5:651-659, 1976.
5. Pape KE, Wigglesworth JS: *Haemorrhage, Ischaemia and the Perinatal Brain*. Philadelphia, JB Lippincott Co, 1979.
6. Lou HC, Lassen NA, Friis-Hansen B: Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 94:118-124, 1979.
7. Volpe JJ: Neonatal intracranial hemorrhage: Pathophysiology, neuropathology and clinical features. *Clin Perinatol* 4:77-102, 1977.
8. Gilles FH, Price RA, Kevy SV, et al: Fibrinolytic activity in the ganglionic eminence of the premature human brain. *Biol Neonate* 18:426-431, 1971.
9. Lazzara A, Ahmann PA, Dykes FD, et al: Clinical predictability of intraventricular hemorrhage in preterm infants. *Pediatrics* 65:30-37, 1980.
10. Mantovani JF, Pasternak JF, Mathew O, et al: Failure of daily lumbar punctures to prevent hydrocephalus following intraventricular hemorrhage. *J Pediatr* 97:278-281, 1980.
11. Volpe JJ, Pasternak JF, Allan WC: Ventricular dilation preceding rapid head growth following neonatal intracranial hemorrhage. *Am J Dis Child* 131:1212-1215, 1977.

'Teach a Man to Fish' (Chinese Proverb)

A number of commentaries have been published by physicians who have worked with Cambodian refugees. The dimensions of that human tragedy, sensationally, if tardily, emblazoned into our consciousness by the press last fall, elicited a remarkable and heartening response from the world community, a response that greatly alleviated the impact of the massive, acute starvation. Medical personnel from many countries participated in this effort. I was part of a team of two physicians and three nurses, sponsored by the American Baptist Convention, which served in Kamput, a small camp in southeast Thailand. Following are a few personal reflections on this uniquely moving experience.

We arrived in Kamput in early January 1980 after the horrendous death rate due to acute starvation had abated. Some sequelae of malnutrition persisted among the Khmer Rouge who populated Kamput, but its most devastating impact was apparent only when the "population pyramid" of the survivors in the camp was examined. Less than 2% of the population was under 5 years of age, less than 5% under 12. Those too young or too old to have made the harrowing journey under their own power through mountains, jungle, and Vietnamese guns, or too heavy to be carried, did not survive. Those who had been severely malnourished when they arrived were either improved, or dead. Therefore, most of those remaining were likely to be fundamentally robust adolescents and young adults with very few chronic diseases—a grizzly illustration of the principle of survival of the fittest.

Approximately 20% to 30% of all the medical problems seen during that period were the result of falciparum malaria. Also commonly seen were respiratory or gastrointestinal tract illnesses, parasites, and skin eruptions, particularly scabies. Iron deficiency anemia was the most frequently encountered nutritional disease,

with some patients showing residual signs of kwashiorkor or beriberi, but with only rare instances of xerophthalmia among this vegetable-eating people. Tuberculosis was not as common as had been anticipated, and few tropical diseases were seen, or if they were, they were not recognized, given the diagnostic limitations of that very basic facility.

After observation of hundreds of outpatients during a few weeks, certain unexpected patterns of complaints began to emerge. Relatively trivial respiratory symptoms, objectively unverifiable "swelling" of legs, headaches already under treatment by square patches of tape over the temples, and vague complaints of fatigue and abdominal discomfort brought patient after patient to the outpatient facility. Being hampered by the language barrier, our earnest but hastily trained Khmer translators were unable to shed much light on the causes of the complaints, or to transmit our inept efforts at the kind of supportive explanations and advice we would normally use in talking to our patients in this country. We found we had stumbled into a trap. Symptoms were treated with a medication—antihistamines, aspirin, cough preparations, vitamins, or whatever could be rationalized as a justifiable response to the complaint. The message was clear to the patients—if the physicians give a medicine for every symptom, then every symptom must need a medicine. We were essentially giving placebos without that most necessary ingredient of the placebo effect—a physician-patient relationship. Predictably, we generated a "revolving door," which was poorly serving both physicians and patients.

CULTURE LAG

There is no great mystery to the cause of these vague symptoms. As actual survival became less of an issue, depression set in, even in the relative comfort of that camp. Few families are intact. Many had seen their loved ones murdered. Their lives seem purposeless and futureless, and even the immediate is characterized by boredom and punctuated by fear of what "repatriation" may mean for them. The psychosomatic manifestations of depression clearly are not confined to our Western society. However, that does not mean that Western physicians are qualified or even eligible to treat depression in a culture in which they are aliens. The introduction of Western medicine to a people unlikely to have a continued future exposure to its "advantages" raises some serious ethical questions.

This is only one example of the many problems of attempting to reach across the world to "lend a hand." However well-meaning we may be, when we go on short notice in response to an emergency, we go in ignorance. We arrive on the scene as "saviors" from the West, honorably motivated perhaps, but very likely to impose our views and our methods on a people with traditions and perspectives different from our own. When the death rate in camps is one per 1,000 per day because of disease and starvation, as was the case in November 1979, the skills, energies, and resources needed are the lifesaving ones. Once the situation is more subacute and chronic, we need to look carefully at more subtle issues if we are genuinely intent on being of help. There must be sensitivity and respect for the history, culture, and beliefs of the people we are serving and an understanding of the genesis of their current situation. For example, the Khmer Rouge, whether guerrillas or unwilling followers, are uneducated peasants, brutalized, both as perpetrators and victims, by an extraordinary complexity of political events about which they have little knowledge and over which they have no control.

Historically, the ethnic Khmer are a gentle, hospitable people, at one time in their early history the dominant and most sophisticated culture of Southeast Asia; but for 800 years, they and their neighbors have been in conflict. In this century, Western intrusion has complicated their circumstances. Our military incursions played a major role in the disruption of that nation's agriculture, in the creation of millions of refugees, and in the preparation of the ground for takeover by Pol Pot's forces and the virtual destruction of the society. Not to have some knowledge of these factors is not to understand the individual Khmer who emerges from the Kampuchean jungle and the Vietnamese artillery fire 11 km away, a hostile, suspicious, and frightened adolescent, who in a short lifetime has seen and been personally involved in horrors most of us cannot imagine.

We must also appreciate the apprehension of the unwilling host country, Thailand, with its own enormous economic problems and medical needs. For whatever humanitarian reasons, world opinion forced them into a position of harboring an ancient foe, with a concern that another ancient foe, the Vietnamese, would use the sanctuaries as an excuse to invade Thai territory in pursuit of their Khmer Rouge quarry. In close proximity to their own desperately needy peasant villages, the Thai see the Khmer being well-fed and ministered to by the world community. International organizations do not have the mandate to render aid to the Thai. However, voluntary agencies were free to do so, and our own team, with the aid of the Thai Marines and Thai Red Cross, established a traveling outpatient clinic that visited some dozen Thai villages near the Kampuchean border on a rotating basis, but this effort could be little more than gestural considering the dimensions of the need.

The host countries in this "age of the refugee" are indeed in a dilemma. As the world's interest flags, they are likely to be left with the responsibility of supporting a population of homeless aliens who are more comfortable in the refugee camps than in their own, still tumultuous villages back home. The sometimes ruthless efforts by the host to make life less comfortable, or to force repatriation despite its certain hazards to the refugees, should not be entirely beyond our understanding even though it may offend our sense of humanitarianism.

FUTURE MEDICAL RESPONSES

Some questions are being raised about the improvisational nature of the medical response to such emergencies. There were problems at the high-

er administrative levels that proved frustrating to those at the actual interface with the refugees, where there was good cooperation among agencies, and where an international comradery developed that essentially ignored the territorial concerns of higher echelons.

With the experience gained from disasters occurring around the world, some specific procedural and organizational issues should have been already defined, particularly those relative to public health and preventive medicine. At Kamput for example, protocols for immunizations and for the treatment of tuberculosis had to be created as though this were a new and unique situation, with few already established guidelines. Organizations like the International Red Cross have established methods of responding to an acute disaster, but comparable groups are needed to achieve the same kind of structured response during the much longer transitional and rehabilitative period, when social service, educational, vocational, and resettlement issues become the predominant concerns. In generating a medical response to the world's disasters, we must go beyond impulsive and dramatic overseas adventures which, though often enormously helpful, do not address needs beyond those of the immediate, life-threatening crisis. The old Chinese saying, "give a man a fish and you give him a meal, teach a man how to fish and you give him a living," was never more apt. We must establish a means, a sensitivity, an immediate capability to share our enormous wealth of skills and materials effectively and for as long as necessary, in a way which taps the full resources of the population being served while remaining sensitive to its special attributes. The optimal patient-physician relationship, in my view, is one in which both the patient and the physician combine the best of their resources in addressing the problem at hand. We must think in terms of such a therapeutic alliance in our efforts to help less fortunate countries.

Such an informed, responsive posture does not develop in our profession without planning, and this must start at the level of medical education. Most of us are aware that a small percentage of the world's people consume more than half of the world's goods. Most of us know that $100 a person a year is spent on health care in developed countries, and only $1 per person per year is spent in developing countries: that 650 of every million children under 5 years of age die per year in developed countries as compared with 48,000 per million children under 5 in developing countries.[1] It is essential that our medical schools develop an institutional milieu that impresses this kind of stark reality on the consciousness of students and that fosters the development of a broader perspective of the world's medical problems. The student enters medical school idealistic and soon finds he must begin to focus his field of study to more manageable dimensions. With the narrowing of his field, there may be a narrowing of his vision and of his idealism. Lectures and articles are inadequate to counter this trend. There needs to be the possibility for students and residents to become immersed in the mainstream of some of the world's suffering, perhaps working side by side with some of their own faculty, or providing training for individuals from developing countries within their own institutions. Obviously, only a selected few would elect such experiences, but the supportive involvement of the institution establishes a model, and transmits to students and to the community a profoundly important message; that we endow what we teach with the humanity that should characterize our profession.

Can these vital educational concerns, and the devastating medical needs of the world, somehow be brought together in a manner that serves both with dignity and effectiveness? This may well rank beside "what is the future role of the pediatrician" as a question to be addressed in the 1980s.

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Reference

1. Morley D: *Pediatric Priorities in the Developing World*. London, Butterworths, 1973.

Sector Scan Ultrasound Imaging Through the Anterior Fontanelle

Its Use in Diagnosing Neonatal Periventricular-Intraventricular Hemorrhage

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• The ultrasound sector scanner was used to visualize intracranial pathologic conditions in neonates. The scan head is small enough to make good contact with the anterior fontanelle of infants as small as 700 to 800 g. Clotted blood is clearly seen as a white, echo-dense area, and the scan quality approaches that of computerized tomographic (CT) scan in neonates with intracranial hemorrhage. Three cases were analyzed with CT scan or by autopsy correlation of sector scans. Clinical applications include the diagnosis of periventricular-intraventricular hemorrhage, posthemorrhagic hydrocephalus, and other intracranial pathologic conditions. The use of ultrasound in the diagnosis of neonatal intracranial hemorrhage is briefly reviewed.

(*Am J Dis Child* 134:1028-1031, 1980)

The detection of periventricular-intraventricular hemorrhage has become a major problem in neonatology.[1,2] Prospective studies using computerized tomographic (CT) scans have shown the incidence of hemorrhage to be approximately 40% in all infants of less than 35 weeks' gestation.[3,4] The diagnosis of hemorrhage is made urgent by the high incidence of posthemorrhagic hydrocephalus and the fact that the extent of hemorrhage has been shown to correlate with prognosis.[5] Thus, detection of hemorrhage at an early stage may allow early therapy for hydrocephalus and may aid in decision making in treatment of severely ill infants.

The diagnosis of hemorrhage is difficult since clinical signs can be absent even in the face of moderate to marked hemorrhage. Although CT scanning reliably demonstrates hemorrhage, it is expensive and exposes the critically ill infant to unneeded risks. For these reasons, we have been interested in finding alternate methods of detecting periventricular-intraventricular hemorrhage.

For editorial comment see p 1023.

Recently, reports have appeared describing linear-array, real-time ultrasound scanning in preterm infants.[6-8] The resolution of published images, however, is limited by bone artifact. Cooke[9] suggested that better resolution could be obtained using the sector scanner and imaging through the anterior fontanelle.

Because the scanner is portable, the scan can be done without disturbing the infant at bedside. In addition, the infant's movements do not detract from the image quality. Thus, the problems of transportation, support, sedation, and exposure to ionizing radiation inherent in CT scanning are avoided. The image quality seems superior to published examples of linear-array ultrasound scans and promises to be as accurate as CT scanning in establishing the presence and extent of hemorrhage. We report our experience in using the sector scan in three illustrative cases with autopsy or CT scan correlation of all sector scans.

MATERIALS AND METHODS

Sector scans were performed at bedside with a real-time digital scan controller using the 5-MHz, three-crystal arc scan head. All scans were done through the anterior fontanelle, with the scan head directly touching the fontanelle after ultrasonic gel was applied. The sector scanner sweeps a field subtended by a 90° arc to varying tissue depth with three rotating pulser receivers. It produces a real-time, two-dimensional image that is recorded on videotape. The scan head is small compared with linear-array transducers. An area as small as 1 sq cm will produce good contact.

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This allows one to use the anterior fontanelle of even 700- to 800-g infants. By changing the plane of the scan head, coronal and sagittal images of high resolution that are devoid of bone artifact can be obtained. Scan time was usually five minutes for both a coronal and a sagittal sweep. The scan was recorded on videotape, and various portions were freeze-framed to make illustrations for this article. The CT scans were obtained in the radiology department.

Hemorrhage is demonstrated by its echo density and by the mass effect it produces. When clotted blood is present, a white, echo-dense area is noted. Prior to clot formation, blood is not as white but makes the ventricular walls indistinct by its intermediate echo density. Periventricular blood can be distinguished not only by its density but by displacement of the walls of the ventricle.

Early in our experience, we correlated the location and size of the hemorrhage shown in the ultrasound images with CT scans or with autopsy in each infant in whom abnormal findings were made. After the first six infants, we no longer believed that this was necessary since hemorrhage and intracranial anatomy were clearly demonstrated by sector scan. We could reliably identify normal structures by their position or their vascular pulsation. The lateral ventricles, interhemispheric fissures, and Sylvian fissures were immediately apparent. In addition, we routinely saw the pericallosal arteries, the cavum septum pellucidum, the third ventricle with its infundibular and chiasmatic recesses, and the fourth ventricle. Certain structures produce increased echoes resembling clotted blood. The structures most likely to produce confusion with periventricular hemorrhage are the head of the caudate and the lateral nuclei of the thalamus. These are echo-dense periventricular structures.

PATIENTS

The three illustrative cases were taken from a group of 62 infants who were admitted to the Maine Medical Center Neonatal Intensive Care Center (MMC-NICC), Portland, between September 1979 and January 1980. We performed a total of 103 scans on these infants for diagnosis and follow-up observation of periventricular-intraventricular hemorrhage. Forty-eight infants were of 35 weeks' gestation or less, and 29 weighed 1,500 g or less. Fourteen full-term infants were also scanned.

We detected 12 hemorrhages in this group, ranging from mild periventricular to large periventricular and intraventricular hemorrhage (grades 1 to 4 of Papile et al[3]). Posthemorrhagic hydrocephalus occurred in four. Three infants died. Other diagnoses made with the sector scan in this group included congenital hydrocephalus in two infants and multicystic encephalomalacia in one.

REPORT OF CASES

Case 1.—A 1,360-g female infant of 30 weeks' gestation was transferred to the MMC-NICC on the first day of life. She had Apgar scores of 0 and 1 at one and five minutes of age. On arrival, the infant had an ashen color but had spontaneous movements. Despite vigorous support, the infant had become stuporous by 18 hours of age and frequent seizures had developed. A sector scan of the brain at 24 hours of age showed bilateral intraventricular hemorrhages. Support was discontinued with parental consent and the infant died. Autopsy confirmed the findings on sector scan (Fig 1 and 2).

Case 2.—A 1,120-g female infant of 30 weeks' gestation was transferred to the MMC-NICC within one hour of birth. The Apgar scores were 4 and 6 at one and five minutes of age. On arrival, the infant appeared to be in mild respiratory distress with good peripheral perfusion. On day 2 of life, a lumbar puncture produced bloody, mildly xanthochromic CSF with an elevated protein level. Sector scan and subsequent CT scan demonstrated a large right-sided periventricular-intraventricular and intracortical hemorrhage (Fig 3). Physical examination revealed a vigorous, alert infant without signs of increased intracranial pressure. By 16 days of age, rapid increase in head circumference was noted. Dramatic hydrocephalus was demonstrated by sector scan and was confirmed by CT scan. External CSF drainage was obtained with a right frontal percutaneous ventricular catheter and a sterile collecting bag. The ventricular size, CSF protein content, and cell count decreased during drainage. After seven days the catheter was removed to avoid infection. The ventricular size increased serially over three days as demonstrated by sector scan, and a ventricular catheter was reinserted (Fig 4). The infant required four separate periods of ventriculostomy drainage, with three to five days between without a catheter. This allowed her to grow to 2.4 kg, and a permanent ventriculoperitoneal shunt was placed.

Case 3.—A 1,630-g infant of 32 weeks' gestation was transferred to the MMC-NICC on the first day of life because of respiratory distress. The infant's twin had been delivered vaginally, but the birth canal had become obstructed by the placenta, so this infant had been delivered by emergency cesarean section. Apgar scores were 7 and 9 at one and five minutes of age. On arrival, the infant was in mild distress. On day 3 a sector scan was performed; the area of the head of the caudate nucleus was indistinct, though no hemorrhage could be seen. The scan was repeated at 10 days of age, and a clot was now apparent in the area of the right caudate nucleus (Fig 5 and 6).

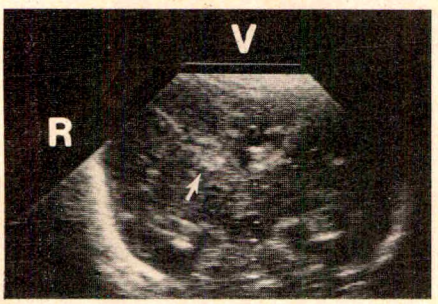
COMMENT

Evidence for the importance of neonatal periventricular-intraventricular hemorrhage comes from recent prospective studies. Papile et al[3] performed CT brain scans on all infants weighing less than 1,500 g during a six-month period. They demonstrated that 43% (20/46) had detectable hemorrhages and graded the hemorrhages by the extent and location of the blood. Clinical evidence of hemorrhage (change in muscular tone and activity, seizures, full fontanelle, hypotension) was more common in infants who died, but some infants with severe hemorrhages survived and had no clinical evidence of hemorrhage.

Similarly, Lazzara et al[4] performed CT scans on all premature infants in their group with a gestational age of less than 35 weeks. They found that 38% (31/81) had hemorrhages. Only half were suspected clinically, and the clinical suspicion of hemorrhage was correlated with marked hemorrhage.

The incidence of posthemorrhagic hydrocephalus in these infants was also studied. Papile et al[3] found that hydrocephalus developed in 44% and Ahmann et al[10] found a 26% incidence of this complication. It was possible to further grade the infants who had hydrocephalus by the extent of the original hemorrhage. Papile et al found that hydrocephalus developed in no infants with grade 1 or 2 hemorrhage, but all surviving infants with grade 3 or 4 hemorrhage demonstrated this complication.[3] Ahmann et al found that the original hemorrhage in those infants in whom hydrocephalus developed was marked in 75%, moderate in 15%, and mild in 5%.[10]

Thus, hemorrhage is common, clinically silent for the most part, and frequently associated with hydrocephalus. The studies cited suggest that



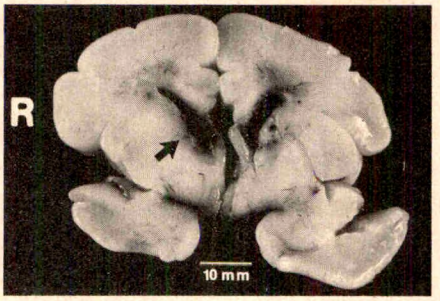


Fig 1.—Left, Coronal sector scan done at 24 hours of age in case 1. V indicates vertex, R, right side. Increased echoes can be seen in right lateral ventricle and periventricular area (arrow). Left lateral ventricle also has increased echoes in it and possibly also in periventricular area. It is not completely obscured, and echo-free area of normal ventricle is noted. Area of third ventricle is deformed and indistinct with increased echoes compared with surrounding brain suggesting that it, too, is filled with blood. Compare with figure on right for anatomical landmarks. Right, Autopsy specimen at approximately same plane as sector scan, left. Note periventricular hemorrhage inferior to right lateral ventricle (arrow). Third and both lateral ventricles contain blood clots.

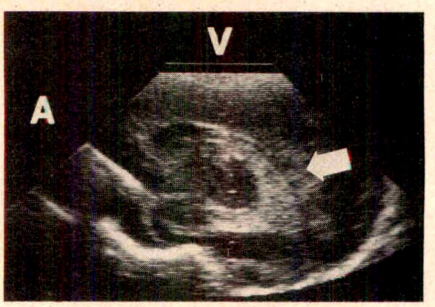
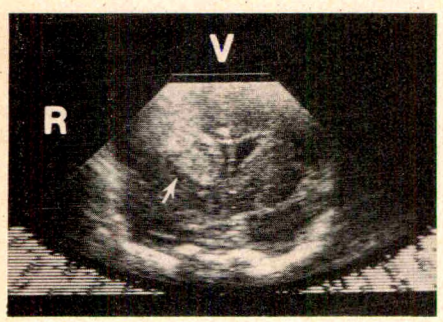


Fig 2.—Sagittal sector scan; image was obtained by angling scan head from anterior fontanelle toward infant's right until sweep of entire right lateral ventricle was seen. V indicates vertex, A, anterior. Note that walls of dilated right lateral ventricle are clearly seen from frontal horns to occipital and temporal horns (arrow). Ventricle is almost completely filled with blood, producing increased echoes.



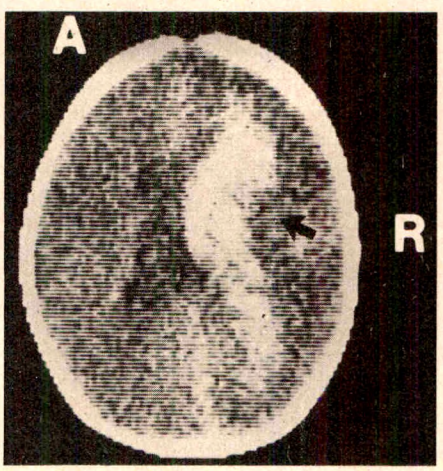


Fig 3.—Left, Coronal sector scan obtained on third day in case 2. V indicates vertex, R, right side. Large periventricular, intraventricular, and intracortical clot can be seen as area of increased echoes in right hemisphere (arrow). Left ventricle is free of echoes and is dilated. Right, A indicates anterior. Computerized tomographic scan obtained same day shows large right-sided hemorrhage and dilated left ventricle (arrow).

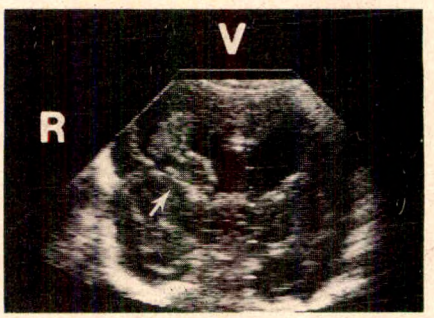
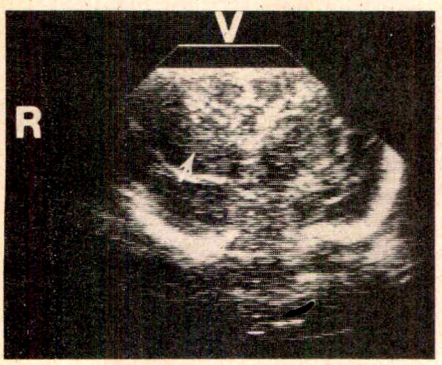


Fig 4.—Coronal sector scan obtained at time of insertion of second ventricular catheter in case 2 (see "Report of Cases"). V indicates vertex, R, right side. Compare with Fig 3, left. Ventricles are dilated and right ventricle shows resorbing clot and developing porencephalic cyst (arrow). Computerized tomographic scan done same day failed to reveal clot.



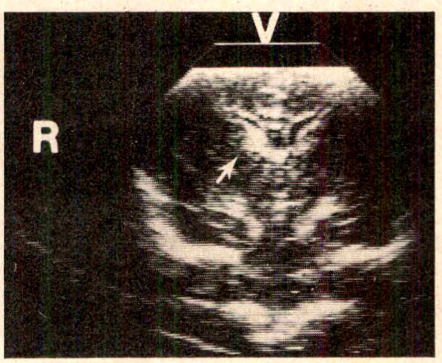


Fig 5.—Left, Coronal sector scan obtained day 3 in case 3. V indicates vertex, R, right side. Area of caudate head (lateral margin of ventricles) is indistinct and ventricles are obscured bilaterally (arrow). Right, Repeated scan obtained on day 10 in case 3 shows clot in periventricular area, now an area of increased echoes (arrow). Right lateral ventricle is mildly deformed by mass effect.

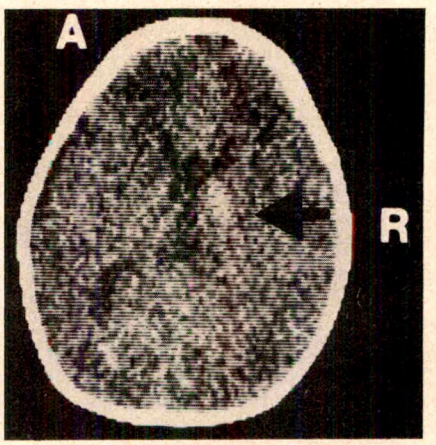


Fig 6.—Computerized tomographic scan in case 3. A indicates anterior, R, right side. Small periventricular hemorrhage seen on sector scan is apparent, right (arrow).

this complication would occur in more than 10% of all neonates of less than 35 weeks' gestation. Although the procedure of CT scanning established these data, its general application to all neonates of less than 35 weeks' gestation has not, to our knowledge, occurred, and recent investigators have looked for other methods of imaging.

Pape et al[6] recently reported their experience in using linear-array, real-time ultrasound scanning in 31 infants of less than 33 weeks' gestation. Dense opacities filling the ventricular system developed in four infants and were confirmed to be hemorrhages by CT scan and by autopsy. Johnson et al[7] studied 41 premature infants, using linear-array, real-time ultrasound scanning and correlated their findings with CT scan. Not all patients had both studies performed, and in only four patients was intraventricular blood clot demonstrated by linear-array ultrasound. Johnson et al did find a high correlation ($r = .99$) between CT scan and ultrasound measurements of ventricular size in 12 infants in whom post-hemorrhagic hydrocephalus developed. Silverboard et al[8] prospectively studied the correlation between linear-array ultrasound and CT scans in 40 infants. Sixteen had hemorrhages that were diagnosed by CT scan (8 marked, 5 moderate, and 3 mild). Ultrasound scan predicted the hemorrhage in all but two infants with mild hemorrhage. Linear-array ultrasound scan uses a transducer that is too large to make a good fit on the anterior fontanelle of small infants. Most scanning is done through the parietal bone and this introduces artifact.

To our knowledge, ours is the first report to show sector scan ultrasound images of periventricular-intraventricular hemorrhage. Our three cases provide evidence for excellent correlation between sector and CT scans as well as for the actual pathologic conditions seen at autopsy. What is more, as mentioned in the legend to Fig 4, the sector scan can show clots that are "isodense" on CT scan. The periventricular region is well seen on the sector scan, but other areas of white matter and of cortex are better visualized by CT scan. Thus, sector scanning has not supplanted CT scanning at our hospital except in screening for periventricular-intraventricular hemorrhage.

We have not prospectively demonstrated that sector scanning is as accurate as CT scanning in instances of mild hemorrhage (ie, hemorrhages confined to the periventricular area). Still, case 3 illustrates such a hemorrhage on sector scan in the head of the caudate nucleus. As Volpe has emphasized, 75% to 90% of hemorrhages originate in the subependymal germinal matrix at the level of the foramen of Monro and the head of the caudate.[2] This is an area particularly well visualized by the coronal sector scan. Thus, theoretically, sector scanning should provide the accuracy of CT scanning in periventricular hemorrhage. However, as illustrated in case 3, the timing of the scan may be critical.

We believe that we have demonstrated the usefulness of static images obtained by sector scanning. However, the scanning is in fact done in real time, and this offers a further advantage. Pape et al[6] have emphasized the advantages of real-time imaging in neonates. They have noted waxing and waning pulses in the choroid plexus and arteries during the evolution of infarction. Although the implication is that loss of pulses may reflect severe decreases in cerebral blood flow, the study of this phenomenon is only beginning. Bada et al[11] have used Doppler recordings through the anterior fontanelle to study intracerebral vascular resistance in asphyxiated neonates. Interestingly, they found decreased resistance to flow in the first 48 hours of life that changed to increased resistance at the time of hemorrhage in preterm infants.

Other research uses that have occurred to us would take advantage of the possibility of doing multiple scans at frequent intervals. This would establish the timing of hemorrhage more accurately and would permit closer scrutiny of various iatrogenic factors such as sodium bicarbonate administration. At present, the sector scanner is being used actively at our hospital to screen all infants of less than 35 weeks' gestation for hemorrhage.

Harold Osher, MD, and Martha Foster, MA, assisted in the preparation of the manuscript.

References

1. Volpe JJ: Neonatal intracranial hemorrhage: Pathophysiology, neuropathology, and clinical features. *Clin Perinatol* 4:77-102, 1977.

2. Volpe JJ: Neonatal periventricular hemorrhage: Past, present, and future. *J Pediatr* 92:693-696, 1978.

3. Papile L, Burstein J, Burstein R, et al: Incidence and evolution of subependymal hemorrhage: A study of infants with birth weights less than 1,500 gm. *J Pediatr* 92:529-534, 1978.

4. Lazzara A, Ahmann PA, Dykes FD, et al: Clinical predictability of intraventricular hemorrhage in preterm infants, abstracted. *Ann Neurol* 4:187, 1978.

5. Krishnamoorthy KS, Shannon DC, deLong GR, et al: Neurologic sequelae in the survivors of neonatal intraventricular hemorrhage. *Pediatrics* 64:233-237, 1979.

6. Pape KE, Cusick G, Houang MTW, et al: Ultrasound detection of brain damage in preterm infants. *Lancet* 2:1261-1264, 1979.

7. Johnson ML, Mack LA, Rumack CM, et al: B-Mode echoencephalography in the normal and high risk infant. *AJR* 133:375-381, 1979.

8. Silverboard G, Horler MH, Ahmann PA: Reliability of ultrasound in the diagnosis of intracerebral hemorrhage and post-hemorrhagic hydrocephalus: Comparison with computed tomographic scan, abstracted. *Ann Neurol* 6:174, 1979.

9. Cooke RWI: Letter to the editor. *Lancet* 3:38, 1979.

10. Ahmann PA, Lazzara A, Dykes FD, et al: Intraventricular hemorrhage: Incidence and outcome. *Ann Neurol* 4:186, 1978.

11. Bada HS, Hajjar W, Chua C, et al: Noninvasive diagnosis of neonatal asphyxia and intraventricular hemorrhage by Doppler ultrasound. *J Pediatr* 95:775-779, 1979.

Reye's Syndrome in Three Siblings

Association With Type A Influenza Infection

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• Reye's syndrome occurred simultaneously in three siblings. All had characteristic changes in liver histology ascertained by light and electron microscopy. The two patients with the most severe disease also had serum that caused marked stimulation of mitochondrial state 4 respiration in vitro. Histocompatibility locus antigen typing showed that no unique haplotypes were shared by all three children. There was no evidence of exposure to aflatoxins, pesticides, or other substances that have been previously postulated to be associated with Reye's syndrome. Influenza A/Brazil/11/78-like virus was isolated from one patient, and all three patients had a fourfold or greater rise in hemagglutination-inhibiting antibody to H1N1 influenza virus.

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Despite reports of increased attack rates of Reye's syndrome for siblings of patients who have the disease,[1] it rarely affects family groups. In the few instances in which multiple cases have occurred in one family, a common, underlying predisposition or a common exposure has been postulated. Pursuing this line of reasoning, investigators have studied histocompatibility locus antigen (HLA) typing,[1] exposure to hepatotoxins,[2-5] and exposure to viral agents[6-9] as possible common factors causing Reye's syndrome to affect siblings. We describe our epidemiologic and clinical investigations of three siblings in whom Reye's syndrome developed concurrently.

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PATIENTS

Table 1 summarizes the illnesses of the three children. Within 24 hours, all had rapid onset of vomiting followed by a change in neurologic status. All three children had an antecedent respiratory illness from which all were uneventfully recovering. Patients 1 and 2 had a more severe illness, which necessitated subarachnoid pressure monitoring and intravenous mannitol to control cerebral edema. After 48 to 72 hours, all three patients showed rapid improvement in clinical status and were discharged after one week of hospitalization. None had any evidence of neurologic deficits at discharge.

MATERIALS AND METHODS

We reviewed hospital records in the referral hospital in Chattanooga, Tenn, from January 1975 to January 1979 to determine the number of patients with Reye's syndrome who were admitted to this hospital. We noted city of residence, date of admission, method of diagnosis, clinical management, and possible relationship to other patients with Reye's syndrome. We interviewed the family members of the three patients and obtained a detailed family medical history for three generations. We questioned family members for any evidence of current family illness and any history of illness that might be compatible with Reye's syndrome.

We visited the three dwellings in which the ill children had stayed for at least one day during the month prior to hospitalization. A careful visual search was made for pesticides, household chemicals, and medicines that might be hepatotoxic. The location of each house in relation to fields that might have been sprayed with pesticides was also determined. We checked the areas near the homes for barns, silos, or other storage facilities that might contain moldy grain or corn and thus be a potential source for aflatoxin. We also visually inspected the water supplies and toilet facilities in the residences under investigation. Sources of heat (ie, coal, wood, gas, charcoal) for these buildings were also investigated to determine whether exposure to potentially noxious gases might have occurred.

Closed percutaneous liver biopsy specimens were obtained on Jan 30 (patients 1 and 2) and 31, 1979 (patient 3) and examined by light and electron microscopy. Biopsies were performed on patients 1 and 2 while they were still comatose. Biopsy was performed on patient 3 one day later to confirm the suspected diagnosis of Reye's syndrome, though her neurologic status did not show the same degree of deterioration as did the neurologic status of patients 1 and 2. All three patients had throat and nasal viral culture taken by swab on Feb 1. Acute- and convalescent-phase serum specimens were obtained on Jan 30 and May 31, respectively, for testing for antibodies to respiratory viruses and were tested by hemagglutination inhibition (HI)[10,11] for antibodies to influenza virus. A fourfold or greater rise in antibody titer was considered diagnostic. Serum specimens from the three children were also tested for their in vitro effect on state 4 respiration (change in nanograms of oxygen released per minute) of a rat's liver mitochondrial preparation. A minor modification of the method of Aprille and Asimakis[12] was used in which 10 μL of a

Table 1.—Summary of Clinical Data in Three Siblings With Reye's Syndrome*

	Patient 1	Patient 2	Patient 3
Age, yr/sex	2½/M	4/M	1⅓/F
Symptoms	Vomiting, lethargy, seizure	Vomiting, lethargy	Vomiting, lethargy
Antecedent illness	Cough and coryza for 1 wk	Cough and coryza for 5 days	Cough and coryza for 1 wk
Neurologic findings on admission	Comatose, flexor responses to deep pain	Comatose, flexor responses to deep pain	Lethargic, responsive to verbal commands
Admission laboratory test results SGOT, IU/L (normal to 18 IU/L)	782	432	732
SGPT, IU/L (normal to 26 IU/L)	804	1,047	555
Blood ammonia, μg/dL (normal to 70 μg/dL)	492	282	52
Prothrombin time, s	18	15	13
Control, s	12	12	12
Serum glucose, mg/dL	24	84	90
Clinical course	Comatose for 48 hr, followed by rapid improvement	Comatose for 72 hr, followed by rapid improvement	Lethargic for 48 hr, followed by rapid improvement
Outcome	Discharged	Discharged	Discharged
Neurologic sequelae	None	None	None

*Patients 1 and 3 had onset of symptoms on Jan 28, and patient 2 on Jan 27, 1979. All three were admitted to hospital on Jan 29, 1979.

Table 2.—Results of Acute- and Convalescent-Phase Serum Specimen Analysis*

	A/USSR/92/77 Specimen		A/Brazil/11/78 Specimen		B/HK/5/72 Specimen	
Patient	1 (Acute)	2 (Convalescent)	1 (Acute)	2 (Convalescent)	1 (Acute)	2 (Convalescent)
1	< 10	40	< 10	40	< 10	10
2	10	40	< 10	20	10	10
3	< 10	40	< 10	40	< 10	< 10

*For hemagglutination-inhibiting factor titers to influenza virus. Values are expressed as nanograms of oxygen released per minute.

fivefold-concentrated serum specimen was placed in 2 mL of incubation medium. Blood specimens obtained from the three children and their father were tested for lymphocyte stimulation using several mitogens, including phytohemagglutinin, pokeweed mitogen, and *Candida*. Levels of serum immunoglobulins were measured, and HLA typing[13] was also performed on the three children and their father. Blood and urine samples from all three children were also tested for the presence of barbiturates, salicylates, heavy metals, and phenothiazines.

RESULTS

Excluding the three siblings in this report, eight cases of Reye's syndrome were diagnosed since 1975 at the referral hospital. Only two of these children were from the same geographic area as the children discussed in this report. Four of the eight children had died. Four cases were associated with chickenpox, and none had occurred in siblings.

A detailed family medical history did not identify any children in the extended family with an illness compatible with Reye's syndrome. There had been only one unexplained death in the past three generations, and the history was compatible with sudden infant death syndrome.

The three homes examined had public water, indoor toilet facilities, and natural gas for heating. No pesticides or common household cleaning agents were located in any cabinets accessible to the children. No family members were taking any prescription drugs, and other medications were kept in a locked cabinet. There were no cultivated fields in the immediate vicinity of any of the homes. There were no barns, silos, or other storage facilities for grain or other material that might have been a source of aflatoxin exposure.

Light microscopic examination of all three liver biopsy specimens revealed microvesicular fatty infiltration. Electron microscopy revealed mitochondrial swelling in all three specimens, but only specimens from patients 1 and 2 revealed mitochondrial disruption. When serum samples from the three patients were tested for in vitro stimulation of state 4 mitochondrial respiration, the two patients with the most severe abnormalities seen clinically and by electron microscope (patients 1 and 2) were found to be stimulatory. The same preparation of isolated rat's liver mitochondria was employed to obtain valid comparisons. In four control subjects, the increase in state 4 respiration was 0.10 ± 0.10 ng of O_2 per minute (mean ± 1 SD); in patient 1 it was 0.94 ng/min; in patient 2, 2.35 ng/min; and in patient 3, 0.24 ng/min.

Urine and blood toxicologic screening on all three children failed to reveal evidence of drug ingestion. There was no history of salicylate ingestion. Immunoglobulin determinations and results of lymphocyte stimulation studies were normal. Analysis of HLA typing for all family members gave the following results: for the father, A28, B40/Aw24, B "blank"; for the mother (as hypothesized, since she had died), A3, B15/Aw19, B12; for patient 1, Aw19, B12/Aw24, B "blank"; for patient 2, A3, B15/Aw24, B "blank"; and for patient 3, Aw19, B12/A28, B40. No haplotype segregation was evident.

No increase in complement-fixing antibodies to coxsackie virus B types 1 to 5, to adenovirus group antigen, or to *Mycoplasma pneumoniae* was observed in the sera for any of the three patients with Reye's syndrome. All three patients, however, had a four-

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fold or greater rise of HI antibody to the closely related influenza A (H1N1) antigenic variants A/USSR/92/77 and A/Brazil/11/78 when paired, acute- and convalescent-phase serum specimens were tested (Table 2). Influenza A/Brazil/11/78-like virus was isolated from a throat culture of patient 1 taken on the fifth day of illness.

COMMENT

We have reported the simultaneous occurrence of Reye's syndrome in three siblings. Not only were all clinical and laboratory criteria for Reye's syndrome met as defined by the Center for Disease Control, Atlanta,[14] but all patients had liver biopsies performed with the characteristic findings of microvesicular fatty infiltration on light microscopy and mitochondrial swelling on electron microscopic examination.[15] The two most severely affected patients had mitochondrial disruption on electron microscopic examination of their liver biopsy specimens and also had serum that was stimulatory to state 4 mitochondrial respiration in vitro. Aprille and Asimakis[16] and Lumeng et al[17] have found that sera from patients with Reye's syndrome contain a low-molecular-weight, heat-stable molecule that interacts with site III of the mitochondrial respiratory chain. The degree of stimulation in each of our patients correlated with the clinical severity of illness.

We could find no environmental factors to explain the simultaneous occurrence of disease in the three children. Though toxins and pesticides have been postulated to play a role in the development of Reye's syndrome, we did not discover exposure to chemicals in these patients. Except for the unlikely event of untested C- or DR-locus antigen associations, there is no evidence of haplotype segregation by HLA typing. These findings are in accord with those of Hilty et al.[1]

Clinical history, culture results, and serologic data all indicate that an H1N1 influenza viral infection was the antecedent event common to all three patients. Earlier reports have linked antecedent types A and B influenza infection with the onset of Reye's syndrome.[6-8] During the winter of 1978 to 1979, there was evidence of a nationwide outbreak of type A influenza (H1N1) virus among children and the concomitant appearance of Reye's syndrome in areas of type A influenza activity.[18]

This episode illustrates the necessity for careful search, not only for potential genetic and environmental factors that might predispose one to the development of Reye's syndrome, but also for infectious agents. Obtaining cultures for viral agents and testing acute- and convalescent-phase serum specimens are necessary to a thorough investigation of these clusters. Though there are reports that Reye's syndrome has occurred in contacts of patients with Reye's syndrome,[9] there is no direct evidence that it is a contagious disease. However, as is illustrated by this cluster of cases, a common exposure to an infectious agent may result in multiple cases of the disease in one family. The HLA typing did not reveal haplotype segregation. Though there may be other underlying genetic factors that predispose siblings in some families to acquiring Reye's syndrome, HLA typing was not fruitful in this investigation. Continued investigations of genetic, environmental, and infectious diseases to determine the etiology and pathogenesis of Reye's syndrome are necessary.

References

1. Hilty MD, McClung HJ, Hayes RE, et al: Reye syndrome in siblings. *J Pediatr* 94:576-579, 1979.
2. Pollack JD, Hughes JH, Hamparian VV, et al: The interaction of chemicals and viruses and their role in Reye syndrome. *Chemosphere* 7:551-563, 1978.
3. Crocker JFS, Rozee KR, Ozere RL, et al: Insecticide and viral interaction as a cause of fatty visceral changes and encephalopathy in the mouse. *Lancet* 2:22-24, 1974.
4. Bourgeois CH, Shank RC, Grossman RA, et al: Acute aflatoxin B toxicity in the macaque and its similarities to Reye syndrome. *Lab Invest* 24:206-216, 1974.
5. Olson LC, Bourgeois CH, Cotton RB, et al: Encephalopathy and fatty degeneration of the viscera in northeastern Thailand: Clinical syndrome and epidemiology. *Pediatrics* 47:707-716, 1971.
6. Hochberg FH, Nelson K, Janzen W: Influenza type B-related encephalopathy: The 1971 outbreak of Reye syndrome in Chicago. *JAMA* 231:817-821, 1975.
7. Ruben FL, Michaels RH: Reye syndrome with associated influenza A and B infection. *JAMA* 234:410-412, 1975.
8. Corey L, Rubin RJ, Thompson TR, et al: Influenza B-associated Reye's syndrome: Incidence in Michigan and potential for prevention. *J Infect Dis* 135:398-407, 1977.
9. Glick TH, Ditchek NT, Salitsky S, et al: Acute encephalopathy and hepatic dysfunction: Associated with chickenpox in siblings. *Am J Dis Child* 119:68-71, 1970.
10. Hierholtzer JC, Suggs MT: Standardized viral hemagglutination and hemagglutination-inhibition tests: I. Standardization of erythrocyte suspensions. *Appl Microbiol* 18:816-823, 1969.
11. Hierholtzer JC, Suggs MT, Hall EC: Standardized viral hemagglutination and hemagglutination-inhibition tests: II. Description and statistical evaluation. *Appl Microbiol* 18:824-833, 1969.
12. Aprille JR, Asimakis GR: Reye's syndrome: The effect of patient serum on mitochondrial respiration in vitro. *Biochem Biophys Res Commun* 79:1122, 1977.
13. Amos DB, Bashair H, Boyle W, et al: A simple microcytotoxicity test. *Transplantation* 7:220-223, 1968.
14. Center for Disease Control: Influenza surveillance—Reye's syndrome and viral infections. *Morbidity Mortality Weekly Rep* 23:58, 1974.
15. Partin JC, Schubert WK, Partin JS: Mitochondrial ultrastructure in Reye's syndrome: Encephalopathy and fatty degeneration of the viscera. *N Engl J Med* 285:1339-1343, 1971.
16. Aprille JR, Asimakis GR: A pathogenic role for a serum factor in Reye's syndrome, in Crocker JSF (ed): *Reye's Syndrome.* New York, Grune & Stratton Inc, 1978, vol 2, pp 361-383.
17. Lumeng L, Greene H, Fitzgerald J: The serum factor in Reye's syndrome and its effect on mitochondrial metabolism and function in vitro. *Gastroenterology* 76:1291, 1979.
18. Center for Disease Control: Reye syndrome—United States. *Morbidity Mortality Weekly Rep* 28:97, 1979.

Long-Limbed Campomelic Dwarfism

A Radiologic and Pathologic Study

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• **Comparison of the roentgenographic and pathologic features of a case of classic, long-limbed campomelic dwarfism with those of previously reported cases leads to the conclusion that the bony abnormalities in this disorder are not due to an intrinsic abnormality of cartilage formation or of osteoblast or osteoclast function. Likewise, no defect in bone collagen, ground substance, or mineralization is evident. The bowing of the long bones may be the result of poorly understood muscular stresses operative in utero. Widespread defects in other organ systems are present, with considerable variation from patient to patient. Phenotypic females with the disorder commonly suffer from gonadal dysgenesis. Autosomal recessive inheritance is suggested for a subgroup of these patients, but environmental factors may be causative in some instances.**

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The campomelic syndrome is a rare form of congenital short-limbed dwarfism characterized by prenatal bowing of the long bones of the lower extremities and is associated with a number of other anomalies of the skeletal system and the CNS.[1,2] Khajavi et al[3] have recently shown that this syndrome comprises a heterogeneous group of disorders and have subclassified them into three types: (*a*) long-limbed, or classic campomelic syndrome, in which the "bent" bones are of normal caliber and are moderately shortened; (*b*) normocephalic, short-limbed campomelic dwarfism, in which the bones are strikingly shortened and also too wide; and (*c*) short-limbed campomelic dwarfism with severe craniosynostosis. The nature of the bony abnormalities in the classic campomelic syndrome is controversial, and the mechanisms responsible for the bowing of the lower limbs are unclear. Furthermore, the spectrum of extraskeletal abnormalities in this condition remains poorly defined. We present here the roentgenographic and autopsy findings of a case of long-limbed campomelic dwarfism, together with a detailed consideration of the emerging radiologic and pathologic features of this condition.

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REPORT OF A CASE

The patient, a 2.4-kg male infant of 36 weeks' gestation (by dates), was born to a 25-year-old, primagravida, Nigerian woman. The parents are nonconsanguineous and were born and raised in different parts of Nigeria. The father was 28 years old when the baby was born. The family history was devoid of short stature, birth defects, mental retardation, and neurologic diseases.

The pregnancy was complicated by an upper respiratory tract infection one week prior to delivery and by maternal hypertension without peripheral edema at 34 weeks' gestation, for which the mother took antihypertensive medication. The mother denied alcohol intake or exposure to ionizing radiation during pregnancy. There was also a history suggestive of polyhydramnios; weight gain during pregnancy was 15 kg, and the uterus was felt to be abnormally large. However, the amniotic membranes ruptured before sonography could be done, and vaginal delivery by low forceps was accomplished 16 hours later. The mother was febrile to 38 °C during this period.

At birth, the baby was noted to have multiple anomalies and was transferred to the UCLA Medical Center. At 1 day of age, the infant weighed 2.5 kg, was 36 cm long, and had a head circumference of 34.5 cm (75th percentile). The anterior and posterior fontanels were of normal size. The infant had a peculiar flat facies with micrognathia, a flat nasal bridge, a slightly elongated philtrum, and low-set but normally shaped ears. The intercanthal dis-

Table 1.—Roentgenographically Observed Abnormalities in Classic Long-Limbed Campomelic Syndrome

Abnormality	Frequency in Previously Reported Cases*	Our Case
Enlargement of skull	20/26	–
Facial hypoplasia	23/24	+
Micrognathia	24/24	+
Slender ribs	24/25	+
Eleven pairs of ribs	13/17	–
Absent mineralization of sternum	10/12	+
Hypoplastic scapulas	28/28	–
Kyphoscoliosis	19/23	–
Flattened vertebral bodies	13/18	–
Narrow vertebrae	8/14	–
Poor or absent mineralization of lower cervical spine	17/23	–
Narrow iliac wings	24/24	+
Increased acetabular angles	18/20	–
Poor development of ischiopubic rami	27/28	+
Vertically or laterally slanted ischia	24/25	+
Dislocation of hips	25/28	–
Bowed humeri	4/25	–
Bowed radii	9/23	–
Bowed ulnae	5/20	–
Dislocation of elbows	7/17	–
Radiohumeral synostosis	2/20	–
Bowed femora	32/32	+
Bowed tibiae	31/31	+
Hypoplastic fibulae	28/29	+
Lack of ossification		
Distal femoral epiphysis	19/25	+†
Proximal tibial epiphysis	25/25	+
Talus	16/24	+
Talus and calcaneus	1/21	–

*Refers to patients in 32 cases previously reported where presence or absence of findings could be verified.[1-20]

†Faint ossification of epiphysis seen in postmortem roentgenogram of dissected limb but not in standard roentgenograms.

tance was normal, and there were no ocular abnormalities. Glossoptosis and a midline cleft of the soft palate were noted. The neck appeared short, but no chest deformities were seen, and the spine was straight. Cardiac examination results were normal. The liver was palpable 2 cm below the right costal margin; there was no splenomegaly. Genitalia were those of a normal male with descended testes. Karyotype (performed on lymphocytes) was 46,XY. The anus was patent. The infant was hypotonic, and the Moro, grasp, and suck reflexes were all poor.

Anomalies of the extremities were striking. There was obvious mesomelic shortening of the lower limbs, which were 39 cm long with an upper to lower segment ratio of 2.2 (normal ratio, 1.7). There was pronounced, symmetrical anterior bowing of the tibias with cutaneous dimples over the point of maximal angulation. Less conspicuous bowing of the fibulas and femurs was also noted. There were bilateral varus deformities of the feet. The upper extremities were unremarkable except for mild hypoplasia of the digits and a mild degree of camptodactyly, particularly of the distal interphalangeal joints. Dermatoglyphics were normal.

The baby was in mild respiratory distress and initially required oxygen therapy but was quickly weaned to room air. He continued to have feeding problems secondary to cleft palate and respiratory distress, which appeared to be independent of his glossoptosis. He died at 11 days of age.

ROENTGENOGRAPHIC FINDINGS

The present case manifests many but by no means all of the roentgenographic features described in previous reports of long-limbed campomelic dwarfism[1-20] (Table 1).

Lower Limbs

The characteristic bowing and shortening of the tibiae, fibulae, and femora as observed clinically were confirmed (Fig 1). In comparison with normal standards,[21] all of the long, tubular bones of the lower limbs were severely shortened, the femora by 30% of their normal 50th percentile length, the tibiae by as much as 50% of their normal 50th percentile length, and the fibulae by as much as 70% of their normal 50th percentile length. The femora were sharply bowed anterolaterally near the junction of their proximal and middle thirds. The tibiae were similarly bowed near the junction of their middle and distal thirds. The caliber of both sets of bones remained normal. Along the concave aspects of their curvatures, the bones were extremely dense, being composed of thick spicules oriented along lines of stress in a direction perpendicular to the cortex and radiating so as to converge at the apex of the curve.

Postmortem roentgenography of a dissected lower limb revealed early ossification of the distal femoral epiphysis. The fibulae, though shortened, were not bowed or diminished in caliber. The tali and cuboid bones, which should be ossified to some extent by birth and by 1 month of age, respectively, remained unossified. The calcanei, instead of being pear-shaped, were rectangular and too closely apposed to the tibiae. The metatarsals appeared normal, but the phalanges were too short. Specific views to investigate the varus deformity of the feet were not taken.

Upper Limbs

The humeri, radii, and ulnae, though not bowed and of normal caliber, were shortened by 25% of their normal 50th percentile length.[21] Neither elbow dislocation nor radiohumeral synostosis was present. In the hands (Fig 2), the first and fifth metacarpals and all of the middle and distal phalanges were shortened. Clinodactyly (shortening and in-curving) of the fifth fingers was present.

Spine

The only vertebral abnormality was failure of mineralization of the pedicles of T-6 through T-8. Neither kyphoscoliosis, vertebral flattening, narrowing of the vertebrae, hypoplasia of the lower cervical spine, nor increased interpediculate distances in the lumbar spine[22] were present, though these features had been previously reported in some cases. Abnormal stellate fissuring of the vertebral bodies was not identified; only their normal venous sinus grooves were seen.

Pelvis

The iliac wings were slightly narrowed, but iliac and acetabular angles[23] remained

within normal limits, and the hips were not dislocated (Fig 3). The ischia were oriented in an excessively vertical direction, and the superior pubic rami had failed to mineralize except for a tiny, faint focus of ossification on the left.

Thorax

The ribs were too narrow but numbered 12 pairs. The thorax was of normal shape. The sternum remained unmineralized. The scapulae were not hypoplastic, a finding at variance with all previously reported cases. The larynx and trachea were of normal width (Fig 4).

Skull and Mandible

The skull was not enlarged, but facial hypoplasia was reflected in an interocular distance that was below the tenth percentile for boys 1 year of age or younger.[24] The mandible was mildly hypoplastic (Fig 5).

AUTOPSY FINDINGS

A comparison of the extraskeletal manifestations in our case with those in previously reported cases is given in Table 2.[1-20,25,26] External examination of the body confirmed the presence of congenital abnormalities of the head and extremities as described clinically. There were no abnormalities of the visceral organs. The lungs were congested. The larynx, trachea, and major bronchi were unremarkable. In contrast with several previous reports, the tracheal and laryngeal cartilages were normal. The abnormal CNS findings were absence of the olfactory bulbs, tracts, and striae. Peripheral nerves were histologically unremarkable.

The major muscle groups of the extremities were grossly and histologically unremarkable. Bilaterally symmetrical pretibial skin dimples were noted. They represented depressions within focal bulges of skin and subcutaneous tissue over the apices of the extremely curved tibiae. Histologic examination of the pretibial bulges showed only condensed dermal collagen at this site. The male genitalia were normal both grossly and histologically.

SKELETAL CHANGES

Portions of the skull, lumbar vertebrae, pelvic bones, costochondral junction, humerus, radius, ulna, entire middle finger of the right hand, femur, tibia, and fibula were examined grossly and histologically. Bones of the cranial vault were normal. The tibia was markedly shortened, measuring 43 mm from the center of the proximal articular cartilage to the center of the distal articular cartilage as a straight line. The measurement from the center of the

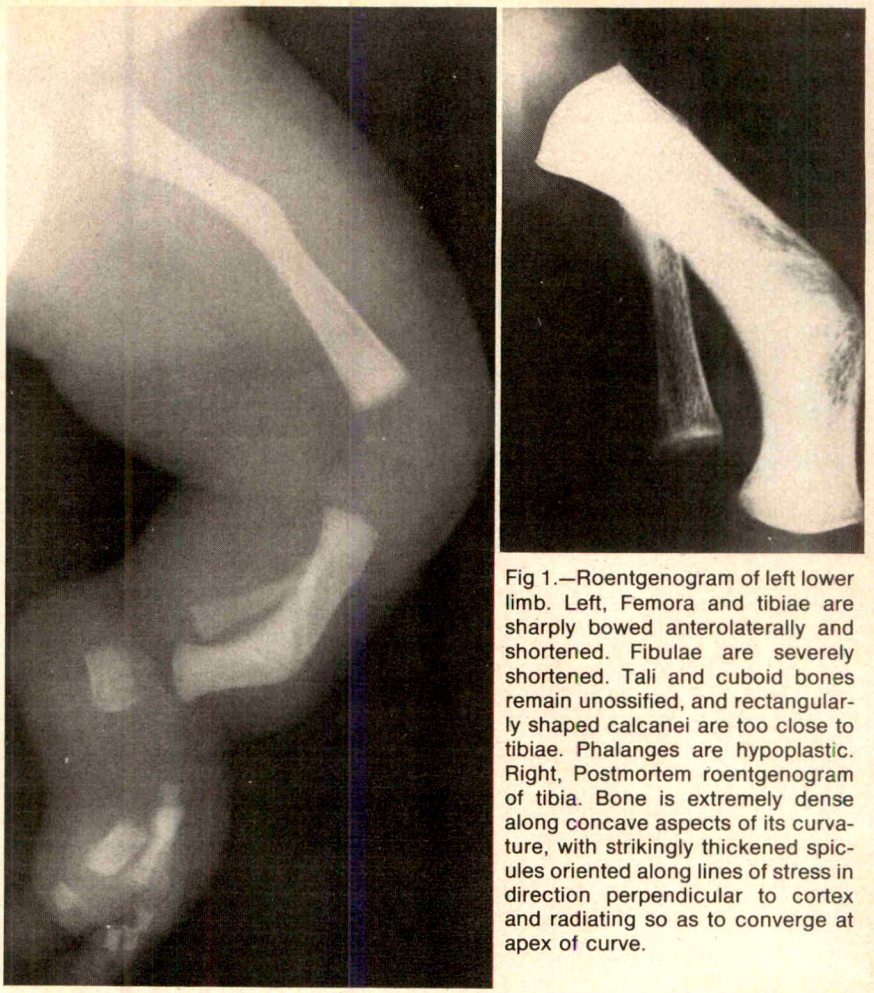

Fig 1.—Roentgenogram of left lower limb. Left, Femora and tibiae are sharply bowed anterolaterally and shortened. Fibulae are severely shortened. Tali and cuboid bones remain unossified, and rectangularly shaped calcanei are too close to tibiae. Phalanges are hypoplastic. Right, Postmortem roentgenogram of tibia. Bone is extremely dense along concave aspects of its curvature, with strikingly thickened spicules oriented along lines of stress in direction perpendicular to cortex and radiating so as to converge at apex of curve.

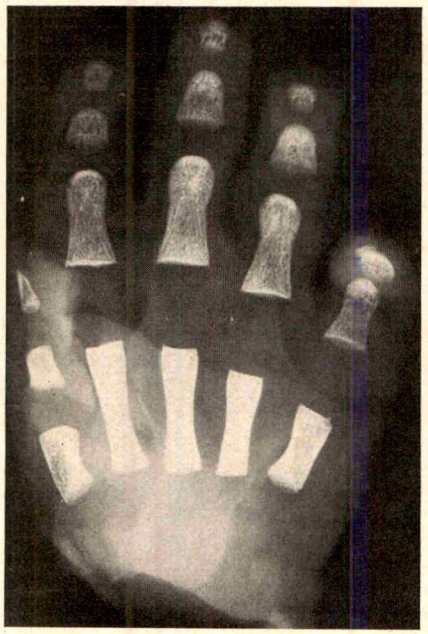

Fig 2.—Postmortem roentgenogram of hand. Shortening of first and left metacarpals, middle and distal phalanges, and clinodactyl of fifth finger.

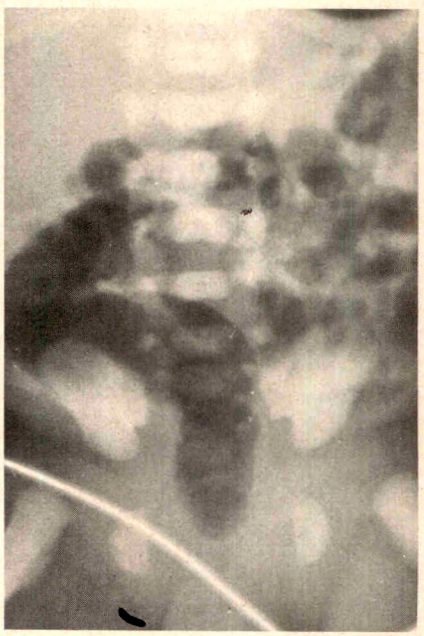

Fig 3.—Roentgenogram of lumbar spine and pelvis. Interpediculate distances are within normal limits. Iliac wings are slightly narrowed. Ischia are excessively oriented in vertical direction. Superior pubic rami have not mineralized.

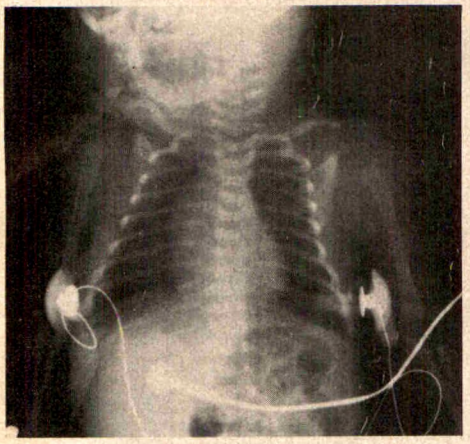

Fig 4.—Roentgenogram of thorax. Ribs are excessively narrow. Shape of thorax is normal. Scapulae are not hypoplastic.

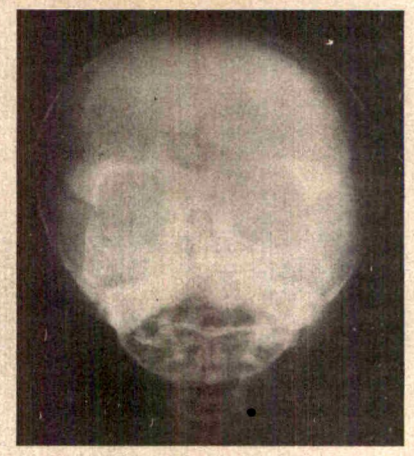

Fig 5.—Roentgenogram of skull and mandible. Anteroposterior view shows severely diminished interocular distance and small mandible.

Table 2.—Extraskeletal Pathologic Findings in Classic Long-Limbed Campomelic Syndrome

Abnormality	Frequency in Previously Reported Cases*	Our Case
Cleft palate	17/28	+
Equinus foot deformities	21/38	+
Malformed or low-set ears	17/38	+
Short, webbed neck	1/38	–
Tracheomalacia (or laryngomalacia)	9/19	–
Deformed hypoplastic epiglottis	1/18	–
Pulmonary hypoplasia	1/18	–
Small thoracic cage and/or tracheobronchial tree	6/18	–
Pneumonia	9/18	–
Pulmonary edema, congestion, and/or hemorrhage	7/18	+
Pulmonary atelectasis	6/18	–
Pleural effusions	2/18	–
Bronchopulmonary dysplasia	1/18	–
Ventricular septal defect	3/18	–
Patent ductus arteriosus	4/18	–
Cardiomegaly	2/18	–
Subendocardial necrosis	1/18	–
Hydronephrosis or hydroureter	5/18	–
Medullary cystic disease	2/18	–
Renal papillary necrosis	1/18	–
Glomerulocystic renal disease	1/18	–
Intestinal malrotation	1/18	–
Pancreatic nesidioblastosis	1/18	–
Atrophy of gastrocnemius muscle	1/18	–
Reduced subcutaneous fat	1/18	–
Left choanal atresia	1/18	–
Cataracts	1/18	–
Abnormal dermatoglyphics	3/18	–
Hydrocephalus or hydromyelia	4/18	–
Absent olfactory nerves, bulbs, tracts	3/18	+
Polygyria	2/18	–
Malformation of caudate, thalamus, or cerebral peduncles	2/18	–
Abnormal aqueduct and fourth ventricle	1/18	–
Large brain	5/18	–
Subdural, subarachnoid, or intracerebral hemorrhage	5/18	–
Granular ependymitis	1/18	–
Periventricular leukomalacia	1/18	–

*Refers to 38 previously reported cases, 18 of which were autopsied.[1-20,25,26]

proximal articular cartilage to the anatomic center of the bone was 27 mm, whereas that from the center of the distal articular cartilage to the anatomic center of the bone was 19 mm. The proximal articular cartilage measured 7 mm in width, and the distal articular cartilage measured 4 mm, at their respective centers. The articular and epiphyseal plate cartilages of the tibia and other bones examined showed no recognizable abnormalities (Fig 6). The columns of cartilage were regular and appeared to be of normal length compared with those of an age-matched control subject. Longitudinal section of the midshaft of the tibia revealed an anterolateral bowing in which long spicules of dense bone originating from the concave aspect of the tibia radiated centrally, creating a pyramidal or dome shape (Fig 7). This abnormal trabecular pattern gradually disappeared in the vicinity of the metaphysis. In cross section (Fig 8), it could be seen that the spicules represented markedly thickened cortical bone with Haversian systems emanating from the posteromedial cortex. The anterior cortex was only 20% of the width of the posteromedial cortex. Because of the marked thickening of the posterior cortex, the central medullary canal of the bone was displaced anteriorly (Fig 8). Examination of the tibial bone using polarized light showed that the types of bone differed from region to region (Fig 9). The radiating bone posteriorly and the extreme apex of bone anteriorly were predominantly of the more immature woven variety, though about 20% of the total bone was lamellar. The lamellar bone was seen about the perimeter of the woven bone scaffold. The remainder of the diaphyseal cortical bone was well-formed lamellar. The bone of the metaphyses and subepiphyseal new bone were predominantly woven. These findings imply that bone formation and/or turnover was greatest in the region of the "bend,"

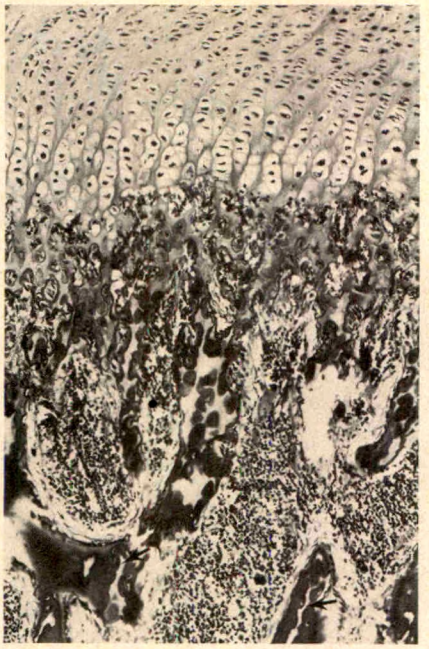

Fig 6.—Photomicrograph of tibial epiphysial plate with columnation. Though degree of columnation may be diminished somewhat, overall configuration of cartilage cells and organization is in sharp distinction to prominent disorganization and lack of columnation seen in achondroplasia. Subepiphyseal bony trabeculae are forming normally and contain central, necrotic cartilage cores (arrows), which represent normal primary spongiosa of infancy (hematoxylin-eosin, ×125).

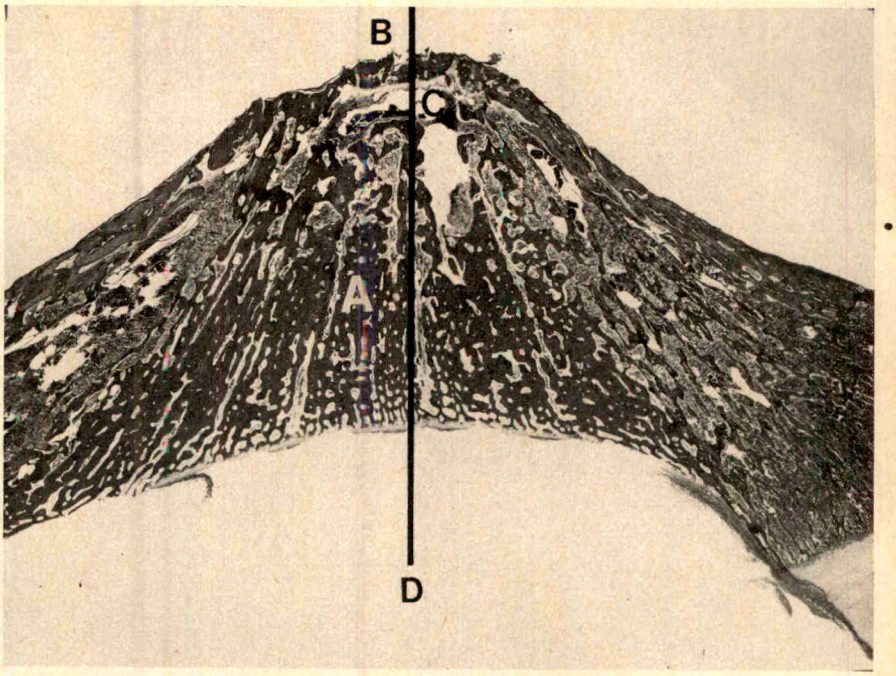

Fig 7.—Low-power photomicrograph of longitudinal section of midshaft of right tibia. Note prominent, centrally radiating spicules of thick trabecular bone (A) that arise from posterior cortex. This bone has no central cartilage cores and presumably arises by appositional growth from periosteum. Note also thin anterior cortical bone (B) over apex of curvature. Anterior portion of bone is more curved than posterior. Central nutritive vessel is displaced anteriorly and eccentrically (C). Metaphyseal areas (extreme right and left of field) do not appear abnormal (hematoxylin-eosin, ×6).

the metaphyseal cortex, and beneath the epiphyseal plate. Though woven bone is to be expected in a child this age in the metaphyses and subepiphyses, the presence of considerable quantities of woven bone at the midshaft bend is abnormal and consistent with abnormal stress to this region. The degree of mineralization of the entire bone appeared normal. The collagen pattern by polarized light examination appeared to be within normal limits, considering the patient's prematurity, except for the region of the bend (Fig 9) and did not resemble the markedly diffuse, woven-bone collagen abnormalities seen in patients with osteogenesis imperfecta in this age group.

Sections of the femora at the sites of their bowing showed changes similar to those described for the tibia. The humeri were not grossly bowed. However, cross section of the midshaft of the right humerus revealed thickening of the anteromedial cortex with evidence of subperiosteal new bone growth. The radii and ulnae were also straight on gross inspection. However, cross section of the diaphysis of the right radius revealed thickening of the anterior cortex with evidence of subperiosteal new bone growth. Mineralization of the bones of the arms and forearms was normal. The bones of the middle finger of the right hand showed no abnormalities of enchondral ossification. The proximal phalanx was normal in length (12 mm), but the middle phalanx was slightly short (6.5 mm in length), and the distal phalanx was hypoplastic (only 1.5 mm in length). Multiple sections through the pelvis revealed no histologic abnormalities of bone and cartilage at this site except for deficiencies in the formation of secondary ossification centers. The lumbar vertebrae appeared normal. The fourth lumbar vertebra measured 6.5 mm in height. The costochondral junction was histologically unremarkable.

COMMENT

Based on the clinical, radiologic, and pathologic findings presented, it is clear that our case falls within the subgroup of campomelic patients that Khajavi et al[3] termed the long-bone or classic type of campomelic syndrome. The relatively long and slender nature of the tubular bones with smooth, nonflared metaphyses and the vertical ischia are important distinguishing features in this regard.

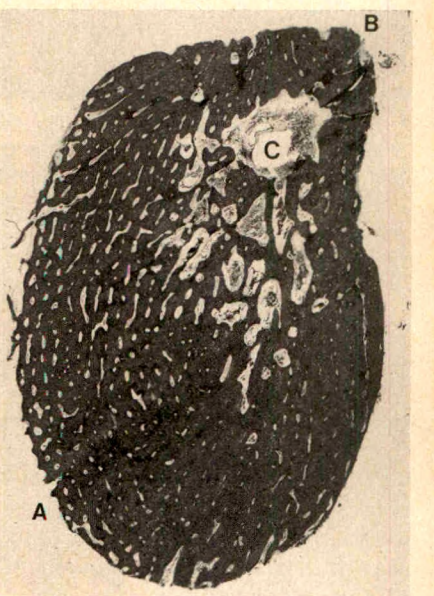

Fig 8.—Low-power photomicrograph of cross section taken through center of tibia (corresponds to line D of Fig 7). Markedly thickened areas of cortex correspond to posteromedial portions of bone (A) and thinner, more normal cortical thicknesses correspond to anterolateral regions (B). Note also anterolaterally displaced marrow cavity with central nutritive vessel (C). (hematoxylin-eosin, ×15).

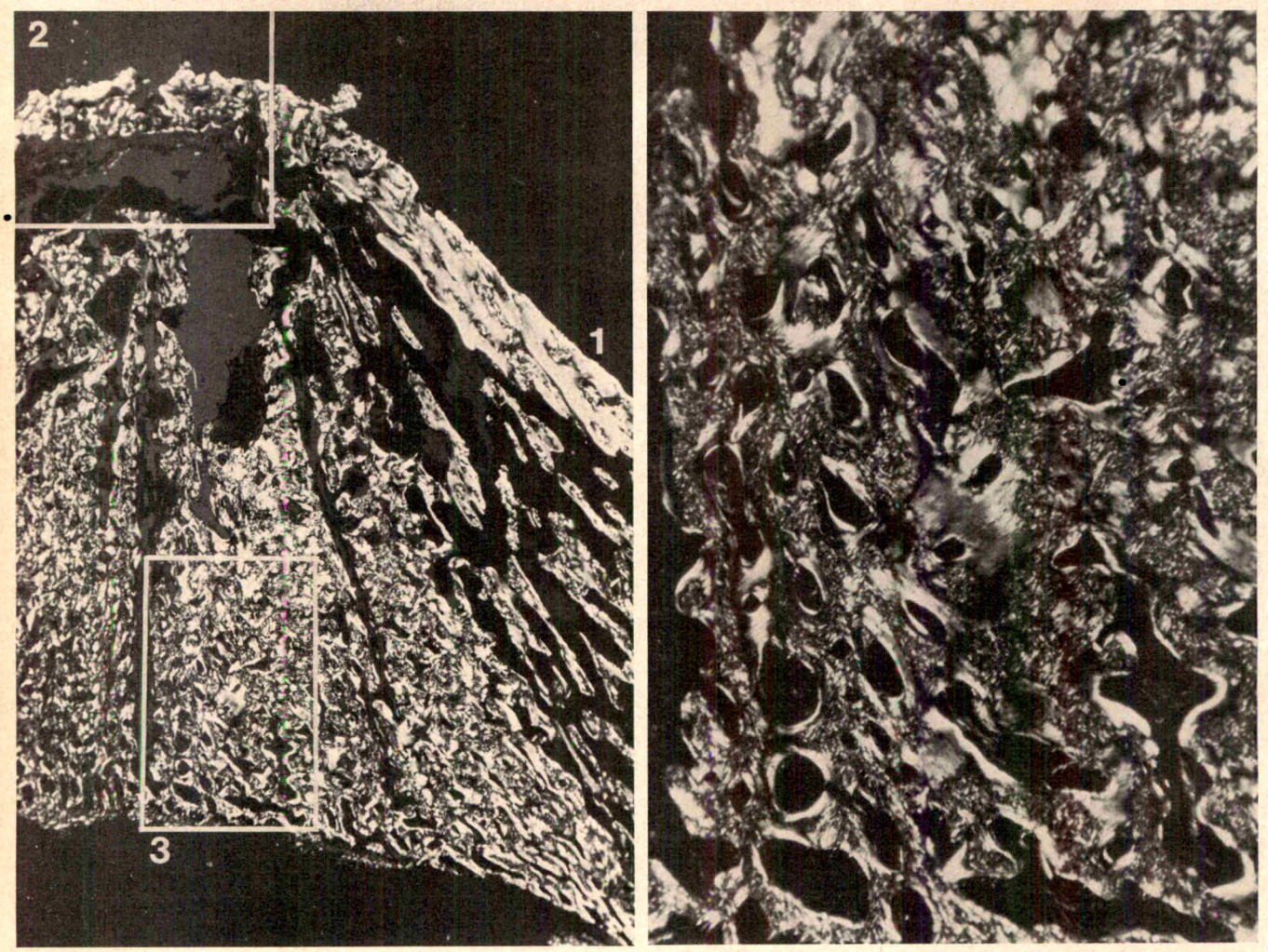

Fig 9.—Photomicrographs of midshaft of tibia under polarized light. Left, Low power showing predominant woven bone pattern along curvature of tibia (insets 2 and 3). Shaft away from area of maximal curvature (1) shows pure lamellar bone pattern (hematoxylin-eosin, ×10). Right, Higher-power view of representative area of thick posterior cortical bone region of bend (inset 3) showing predominantly woven bone with thin covering of brighter, well-oriented lamellar bone (hematoxylin-eosin, ×40).

Bone Abnormalities

Our review of the previously reported cases of the campomelic syndrome has indicated 38 cases[1-20,25,26] (18 of them autopsied) that appear to meet the skeletal criteria for long-limbed campomelic dwarfism. There has been considerable controversy about the nature of the bone abnormalities in long-limbed campomelia. Of the 15 cases prior to our own in which bone histology was reported, eight[1,3,11,16] showed changes similar to those we have described. We interpret those changes as secondary effects and not indicative of a primary abnormality of bone growth. The other seven cases[2,7,17,20,26] were said to show defects in cartilage growth and other abnormalities. To determine whether or not this indicated a heterogeneity in the bone pathology of long-limbed campomelic dwarfism, we have reviewed the available evidence from these cases. Bain and Barrett[7] described acellular cartilaginous cores in some bony trabeculae of the tibia. Our case showed similar bone enveloping dead cores within the metaphysis. It was normal in amount and location and merely represented the normal primary spongiosa of developing infants; it was not evidence of an abnormality of cartilaginous growth as stated in their communication. Lee et al[2] described defects of cartilage proliferation in their cases 1 and 3. The changes in regularity and length of the columns of the cartilage at the epiphyses in case 3 appear minimal to us. In the absence of an age-matched control subject, it is difficult to determine the severity of the irregularity and shortening of the columns of cartilage in their case 1, but the pictures presented do not indicate to us a serious or primary alteration in epiphyseal cartilage growth and maturation. Minor changes, if present, may well be secondary to a more generalized disturbance of uncertain nature.

Case 1 of Hovmoller et al[17] is also supposed to show reduced height of the proliferating and hypertrophic zones of the epiphyseal cartilage, but the example presented in the only

photograph looks essentially normal. Those authors also claimed that the posterior part of the tibial shaft at the site of the bend showed morphologic evidence of low turnover rates. By contrast, histologic examination of our case in normal and in polarized light indicates higher rather than lower turnover in the posterior tibial shaft, as evidenced by the presence of substantial amounts of primitive woven bone, when compared with the normal lamellar bone seen in the diaphyseal cortex away from the region of radiating spicules. Normally, the center of the diaphysis of a newborn is the most lamellar portion of the bone. We interpret the case of Hovmoller et al as showing histology essentially similar to that of our case except for the presence of brown pigment in the intercellular matrix, which they alone have described.

Thurmon and Kityakara[26] described "defective endochondral ossification" in their case 3. Like Bain and Barrett,[7] they described persistence of cartilage within bony trabeculae, which we interpret as the normal primary spongiosa of newborns and infants. We also disagree with their suggestion that a defect in osteoclasts may be responsible for the observed effects. They mentioned that the osteoclast is rich in alkaline phosphatase. Actually, the osteoclast is rich in acid phosphatase and contains no alkaline phosphatase. A defect in osteoclasts should lead to osteopetrosis; campomelic dwarfism bears no resemblance to osteopetrosis. If they meant that there was evidence of an osteoblastic disorder, neither did we encounter evidence to support this suggestion. Mineralization appeared normal on x-ray films, and the strength of the bones appeared normal on gross examination and on sectioning. Good lamellar bone was forming in areas. The two cases of Krous et al[20] are described as showing mild to moderate shortening and some irregularity of cartilage columns at the epiphyses of long bones, but these again lacked age-matched control subjects.

In summary, we find no convincing evidence in our case or in the literature for notable heterogeneity in the pathology of the long bones in this form of campomelic dwarfism. Furthermore, we find no evidence for a defect either in bone collagen, ground substance, or mineralization.

However, in analyzing the in vivo and specimen roentgenograms and the histology of our case in the light of Wolff's law (which states that bone is laid down along lines of compressive or tensile stresses), there is evidence of excessive compressive forces posteriorly in the long bones. This is most severe in the tibia and femur and results in radiating trabeculae of periosteal new bone laid down to resist the stress. The anterior portion of the bend shows a thin cortex that is rich in woven bone consistent with an excess in tensile stress. Such increased stress must be relayed to the bone by the much larger posterior (as compared with the anterior) muscle groups in the thigh and upper leg. Surprisingly, we found, as did Middleton,[4] that the muscles of the extremities are anatomically normal in size and contour. Furthermore, except for the case of Schmickel et al,[12] which was said to show focal atrophy of the gastrocnemius muscle, neither we nor others have detected histologic abnormalities of muscle in campomelic patients.

Nonetheless, the observation that the bones show normal radiologic density and appear to have normal gross breaking and cutting strength, while the osteoblasts appear to have the capacity to form lamellar bone without woven bone in some cortical areas, suggests that the basic abnormality may be increased muscle stress. It is almost as if the long bones were forming normally for a period during embryonic or fetal development, and then at some later stage a change occurred in the muscles (such as shortening or contraction by an unknown mechanism). This effect would be most disproportionate in the larger, dominant muscle groups of the thigh and upper leg. As a result of greater posterior stress on it, the bone would respond by the production of massive posterior periosteal new bone formation and remodeling. The central anterior bowing would result from remodeling to conform to the disproportionate stress applied posteriorly. The frequent finding of equinus deformities of the feet in campomelic patients provides support for such a hypothesis. Also, the presence of anatomic abnormalities of the nervous system accompanied by generalized muscular hypotonia at birth in these infants makes a defect in the tonus of antagonistic muscle groups during development at least plausible. It seems clear that the bowing, which may involve all four extremities, is far too consistent in direction to be merely the result of a chance abnormality of fetal position. The proposed hypothesis of early muscular imbalance might be tested by (1) prompt evaluation of fetal campomelic dwarfism detected through prenatal diagnostic studies and (2) electromyographic studies on cases recognized at birth.

The pathogenesis of the bony abnormalities of the skull and trunk is even more mysterious. However, here again the available evidence suggests no primary abnormality of bone matrix formation or mineralization. The large skull is probably secondary to the large brain size of many of these infants. Vertebral, pelvic, and scapular abnormalities might also be explained by imbalances of muscle tonus similar to those invoked to explain the bending of the long bones.

Extraskeletal Abnormalities

A comparison of the extraskeletal manifestations of our case of campomelia with those in previously reported cases (Table 2) shows both the multisystem involvement and the considerable heterogeneity of findings within the syndrome. Among the most frequent abnormalities are foot deformities and cleft palate. Abnormalities of cartilage involving the ears, tracheal and laryngeal cartilages, and epiglottis are present in about half of reported cases, leading some authors to suggest a generalized defect of cartilage maturation. However, it appears clear that abnormalities of tracheal or laryngeal cartilages do not totally account for the respiratory distress experienced by these patients, since respiratory distress has been a universal feature of the condition in patients with normal as

well as abnormal tracheobronchial trees. The generalized nature of this disorder is further shown by the frequent occurrence of cardiac, renal, and CNS abnormalities. Newborns with campomelia are almost uniformly hypotonic, which may contribute to their respiratory difficulties. Though it is tempting to try to relate the bowing of the long bones to some neuromuscular dysfunction (as aforementioned), no single anatomic abnormality of the CNS has been detected in more than a few cases. It seems likely, however, that many of the autopsied cases did not receive a detailed examination of the brain.

Gonadal Dysgenesis

The reported association of XY gonadal dysgenesis with campomelia is a very interesting one. Of the 39 reported cases, including our own, the sex of the patients is indicated in 35. Nine of these were phenotypically male. Only three males, including our case, have been karyotyped and they show the normal male XY chromosome constitution. Of the 26 phenotypic females, 11 have been karyotyped. Seven of these had an XX sex chromosome complement, whereas four were XY. In addition, we have recently encountered at UCLA twins with campomelia, both of whom were phenotypically female but had 46,XY karyotypes. A possible case of campomelia described by Hovmoller et al,[17] which showed only unilateral tibial bowing, was also a phenotypic female with an XY karyotype. Pathologic examination of the gonads was carried out on four phenotypic males, all of whom showed normal male genitalia, and on 13 phenotypic females. Five XX females and four females who were not karyotyped showed normal ovaries. Of the four XY females examined at autopsy, one had histologically normal-appearing ovaries with occasional, undifferentiated germ cells but no primordial follicles, one had testes, and a third had poorly differentiated ovaries containing some germ cells that were in meiotic prophase as would be expected of XX germ cells. The fourth case showed grossly normal ovaries, as did the possible case of Hovmoller et al,[17] but histologic examination was not performed. Thus, it appears that a subgroup of female campomelic patients have XY gonadal dysgenesis, but that the majority of females with this disease are genotypically XX. From the brief description of the findings in cases of campomelia with gonadal dysgenesis, it does not appear that these patients differ from others in their skeletal abnormalities or in their pattern of associated extragonadal abnormalities.

The etiology of campomelic dwarfism remains unclear. Any theory that would explain the syndrome must take into account the wide spectrum of abnormalities involving many organ systems. The occasional occurrence of the disease in siblings (with the mother showing some stigmata of the disorder in one instance[13]) and the presence of parental consanguinity in another case suggest that a subgroup of the cases may have a genetic abnormality. The finding of a proliferative placental villitis in their case led Krous et al[20] to postulate a viral etiology. It is possible that a variety of noxious agents acting at a susceptible time during gestation is capable of producing this syndrome. In several cases, a variety of drugs had been taken by the mothers of these infants during gestation but these agents were not proven teratogens.

Though much has been learned about this fascinating syndrome, it is obvious that to completely elucidate the basic mechanisms responsible for the morphologic features and symptoms of this disease, further studies are needed. Quantitative analyses of bone strength, mineral and collagen content of bone, muscle histochemistry, and extensive neuromuscular examination of these patients should be performed in future cases of this syndrome.

References

1. Maroteaux P, Spranger J, Opitz JM, et al: Le syndrome campomelique. *Presse Med* 79:1157-1162, 1971.
2. Lee FA, Isaacs H Jr, Strauss J: The "campomelic" syndrome. *Am J Dis Child* 124:485-496, 1972.
3. Khajavi A, Lachman R, Rimoin D, et al: Heterogeneity in the campomelic syndromes: Long- and short-bone varieties. *Radiology* 120:641-647, 1976.
4. Middleton DS: Studies of prenatal lesions of striated muscle as a cause of congenital deformity. *Edinburgh Med J* 41:401-442, 1934.
5. Williams ER: Two congenital deformities of the tibia: Congenital angulation and congenital pseudoarthrosis. *Br J Radiol* 16:371-376, 1943.
6. Bound JP, Finlay HVL, Rose FC: Congenital anterior angulation of tibia. *Arch Dis Child* 27:179-184, 1952.
7. Bain AD, Barrett HS: Congenital bowing of the long bones: Report of a case. *Arch Dis Child* 34:516-524, 1959.
8. Bianchine JW, Risemberg HM, Kanderian SS, et al: Camptomelic dwarfism. *Lancet* 1:1017-1018, 1971.
9. Gardner LI, Assemany SR, Neu RL: Syndrome of multiple osseous defects with pretibial dimples. *Lancet* 2:98, 1971.
10. Cremin BJ, Orsmond G, Beighton P: Autosomal recessive inheritance in camptomelic dwarfism. *Lancet* 1:488-489, 1973.
11. Hoefnagel D, Wurster D, Carey D, et al: Camptomelic dwarfism. *Lancet* 1:1068, 1972.
12. Schmickel RD, Heidelberger KP, Poznanski AK: The campomelique syndrome. *J Pediatr* 82:299-302, 1973.
13. Thurmon TF, de Fraites EB, Anderson EE: Familial camptomelic dwarfism. *J Pediatr* 83:841-843, 1973.
14. Storer J, Grossman H: The campomelic syndrome: Congenital bowing of limbs and other skeletal and extraskeletal anomalies. *Radiology* 111:673-681, 1974.
15. Shafai I, Schwartz L: Camptomelic syndrome in siblings. *J Pediatr* 89:512-513, 1976.
16. Weiner DS, Benfield G, Robinson H: Camptomelic dwarfism: Report of a case and review of the salient features. *Clin Orthop* 116:29-31, 1976.
17. Hovmoller ML, Osuna A, Eklof O, et al: Camptomelic dwarfism: A genetically determined mesenchymal disorder combined with sex reversal. *Hereditas* 86:51-62, 1977.
18. Ameri MR, Alebouyeh M, Amirfeyz M, et al: Das kampomele syndrom. *Monatsschr Kinderheilkd* 126:687-689, 1978.
19. Kozlowski K, Butzler HO, Galatius-Jensen F, et al: Syndromes of congenital bowing of the long bones. *Pediatr Radiol* 7:40-48, 1978.
20. Krous HF, Turbeville DF, Altshuler GP: Campomelic syndrome: Possible role of intrauterine viral infection. *Teratology* 19:9-14, 1979.
21. Maresh MM: Linear growth of long bones of extremities from infancy through adolescence. *Am J Dis Child* 89:725-742, 1955.
22. Simril WA, Thurston D: The normal interpediculate space in the spines of infants and children. *Radiology* 64:340-347, 1955.
23. Caffey J, Ross S: Pelvic bones in infantile mongoloidism: Roentgenographic features. *AJR* 80:458-467, 1958.
24. Hansman CF: Growth of interorbital distance and skull thickness as observed in roentgenographic measurements. *Radiology* 86:87-96, 1966.
25. Hoefnagel D, Wurster-Hill DH, Dupree WB, et al: Camptomelic dwarfism associated with XY-gonadal dysgenesis and chromosome anomalies. *Clin Genet* 13:489-499, 1978.
26. Thurmon TF, Kityakara A: *Camptomelic Dwarfism*. Birth defects original article series, New York, National Foundation March of Dimes, 1974, vol 10, No. 9, pp 89-95.

Nosocomial Scalded Skin Syndrome

Ritter's Disease Caused by Phage Group 3 *Staphylococcus aureus*

Alfred L. Florman, MD, Robert S. Holzman, MD

• **Three cases of generalized exfoliative staphylococcal scalded skin syndrome (SSSS) were encountered during a 25-day period in a nursery for premature infants. A single strain of *Staphylococcus aureus*, phage type 42E/54/75 (group 3), was recovered from each of the three infants and from no others. Two of the three isolates were tested and both produced epidermolytic toxin (ET). Most cases of SSSS have been associated with phage group 2 strains. To our knowledge, this is the first report of a nursery outbreak caused by a phage group 3 staphylococcus. It illustrates that ET production and not phage type distinguishes *S aureus* strains that are associated with SSSS.**

(*Am J Dis Child* 134:1043-1045, 1980)

Staphylococcal scalded skin syndrome (SSSS) has been well described. Despite some superficial similarities and earlier confusion, it now has been differentiated clinically and histologically from drug-induced toxic epidermal necrolysis.[1-3] In 1971, it was suggested by Melish and Glasgow[4] that SSSS be considered a spectrum of rashes that includes a generalized exfoliative disease in infants (Ritter's disease), a generalized scarlatiniform erythema without exfoliation, and bullous impetigo. This was because all of them are caused by an epidermolytic toxin (ET), which up to that time had been exclusively associated with phage group 2 strains of *Staphylococcus aureus*. However, a report from Japan[5] now states that only four of 21 children with SSSS seen during a four-year period had phage group 2 isolates. All others had strains in either phage group 3 or both 3 and 1. We report the first nursery outbreak of the generalized exfoliative form of SSSS (Ritter's disease) associated with a phage group 3 *S aureus*.

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REPORT OF CASES

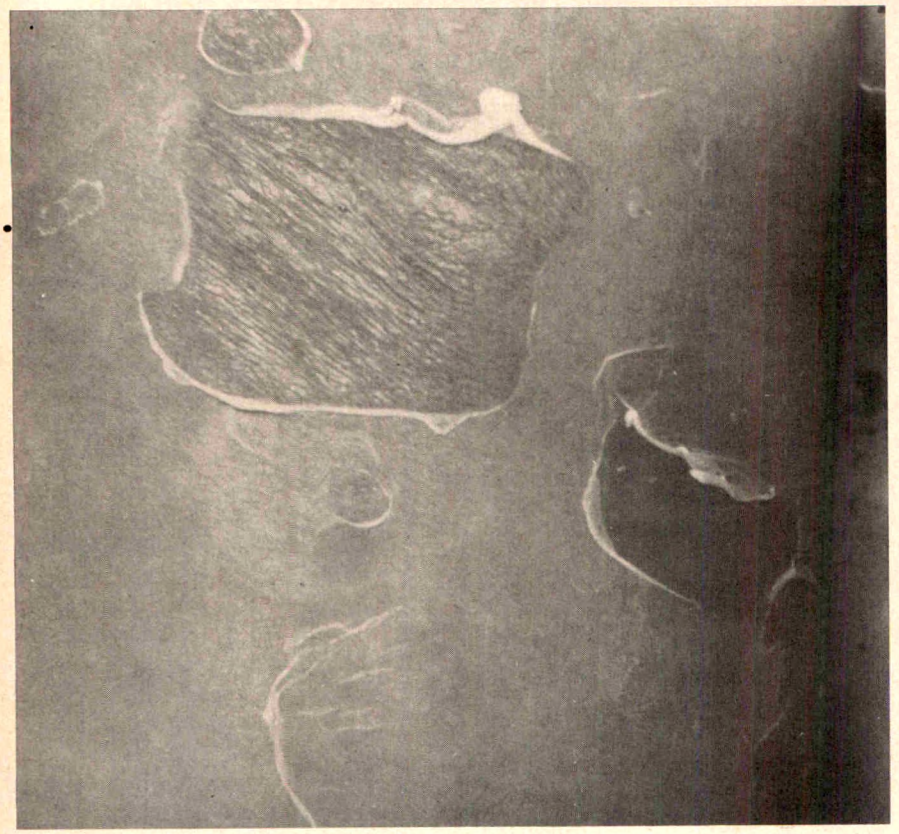
Case 1.—A female infant was born prematurely on March 12, 1979, weighing 2.1 kg. She was cared for in a five-bassinet room (R40) of a six-room special care nursery (SCN), and remained well until 17 days of age, when an erythematous rash was noted first in the perioral area. It quickly spread to involve the entire body. Blisters and desquamation appeared about the mouth, upper eyelids, axillae, vagina, and over the trunk (Fig 1). Despite this, she remained afebrile, alert, and vigorous. The WBC count was 10,900/cu mm, with 46% neutrophils, 13% band forms, 30% lymphocytes, and 5% eosinophils. She was moved from the SCN, placed in isolation, and treated with parenteral oxacillin sodium for ten days. One week later, the skin was clear except for some residual peeling on the hands and feet.

Case 2.—A male infant was born prematurely on March 29, 1979, weighing 2 kg. After 30 hours of care in the intensive care unit (ICU), he was transferred to R40, arriving there 24 hours after patient 1 had left. Because of respiratory distress, he was treated with ampicillin sodium and gentamicin sulfate for the first five days of life. On the 16th day of life, a red rash was noted about the mouth. The rash spread quickly to cover his entire body, and vesicles appeared in the groin. The next day, there was peeling about the mouth. He remained afebrile. His WBC count was 10,500/cu mm, with 29% neutrophils, 17% band forms, 53% lymphocytes, and 1% eosinophils. He was transferred out of the unit, placed in isolation, and treated with parenteral oxacillin and kanamycin sulfate for five days. By that time, the rash had cleared completely.

Case 3.—A male infant was born March 30, 1979, by cesarean section, weighing 1.4 kg. At 5 days of age, he was transferred from the ICU to R40. At 26 days of age, a circumoral rash was noted. The next day, peeling appeared about the eyes and groin. He was afebrile. His WBC count was 7,700/cu mm, with 13% neutrophils, 6% band forms, 71% lymphocytes, 6% monocytes, and 4% eosinophils. He was moved out of the SCN, placed in isolation, and treated with parenteral oxacillin for ten days, with rapid improvement. He had been in R40 with patient 2 for 11 days before that child experienced his rash.

BACTERIOLOGIC FINDINGS

Staphylococcus aureus was recovered from the nose of each of the three



Appearance of rash of patient 1 after 24 hours.

infants. Blood cultures from all three were negative. Isolates were shown to be a single strain both by antibiogram and phage type. They were resistant by disk testing to penicillin, streptomycin, and tetracycline (except that the isolate from patient 3 was sensitive to tetracycline), and all were sensitive to oxacillin, erythromycin, and gentamicin. Isolates from all three infants and from a physician carrier were phage typed using both the international basic set of phages and a number of experimental phages. The staphylococci were phage type 42E/54/75. These phages are in group 3 of the international set. With the New York City Department of Health set of experimental phages, they all were typed as 1141/1135/1127/1049/1976/1136.

TOXIN PRODUCTION

Isolates of the epidemic strain from patients 1 and 2 and from a physician carrier were tested using a suckling mouse assay.[6] All three isolates were shown to produce an ET.

EPIDEMIOLOGIC FINDINGS

It has been the practice to take weekly surveillance cultures for *S aureus* from the anterior nares of all infants in the ICU and SCN. After the first case was diagnosed in the SCN, nose cultures were also obtained from 28 members of the nursing and medical staffs. Although eight had cultures that were positive for *S aureus*, only one isolate, from a house officer, showed the same antibiogram and phage type as the patient. It was impossible to determine if the physician had introduced the organism to the SCN or had acquired it there. However, she left the service 12 days before case 2 was recognized. After the second case, nose cultures were obtained from 26 members of the staff then assigned to the unit. None were found to have the epidemic strain. A review of all surveillance cultures taken in both ICU and SCN from two weeks before the appearance of the first case until two weeks after the third failed to reveal any other infants with this strain. Relatively few environmental cultures were taken. However, on the same day that a surveillance culture from case 2 was found to be positive, the hyperalimentation fluid being given to another infant in that room was also reported as positive for *S aureus*. This culture was obtained prior to passage of the fluid through an in-line filter. Because all cases occurred in the same room (R40), an environmental source was suspected. Consistent with this suspicion, no further cases occurred after R40 was closed to new admissions and all infants in the unit were given a single bath with 3% hexachlorophene. The room was reopened only after the cohort of babies had all been discharged.

COMMENT

In 1878, Ritter described what he called "dermatitis exfoliativa neonatorum" among young infants in a foundling hospital in Prague. Today, this would be recognized as generalized SSSS in neonates. Ritter considered the disease noninfectious.[2] In retrospect, many of his cases must have been nosocomial infections. An association with *S aureus* became clear by the early 1900s.[2] When phage typing became available in the early 1960s, it seemed that only staphylococci in phage group 2 were involved.[7]

In 1952, Lee et al[8] reported what they believed to be the first nosocomial epidemic of Ritter's disease in a nursery in the United States. On the basis of clinical and autopsy findings, they suggested that a staphylococcal toxin might be the cause. It was not until 1970 that Melish and Glasgow,[6] with the use of a suckling mouse model, were able to show that this indeed was so and to partially purify the toxin obtained from phage group 2 isolates. Although group 2 strains have continued to predominate, occasionally non-group 2 strains were recovered from patients in the United States.[9] In Japan, there has been a recent shift to such strains.[5] In 1974, Kondo et al[10] described an ET from non-group 2 strains that elicited the same reaction in suckling mice as did the toxin from group 2 strains. However, it differed serologically and was

more sensitive to heat. They called the toxin obtained earlier from phage group 2 staphylococci "exfoliatin A" and the one from the non-group 2 strains "exfoliatin B." Subsequently, they found that production of ET serotypes (A or B) was not restricted to specific phage types.[11]

At about the same time, Rogolsky et al[12] presented evidence that the gene for production of ET from a phage group 2 strain was located in a plasmid. Since plasmids may be lost easily or transferred, such dissociation of ET production and phage type is not surprising. The phage group 3 strain of *S aureus* isolated from our patients produced ET when it was tested in suckling mice. We do not know whether the toxin was serotype A or B.

In 1976, Faden et al[13] reported a nursery outbreak of SSSS with a scarlatiniform rash caused by an ET from a phage group 1 *S aureus*. That report, together with our experience and that from Japan,[5] serves to illustrate that ET production can occur with phage group 1 and 3 as well as group 2 staphylococci. It is ET production and not phage type that distinguishes *S aureus* strains associated with SSSS. In a susceptible host, this syndrome may be caused by ET producing staphylococci from any of the phage groups.

Samuel Schaefler, PhD, New York City Department of Health, performed the phage typing. Lowell A. Glasgow, MD, Utah College of Medicine, Salt Lake City, tested the isolates of the epidemic strain for ET production.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Alpen-N, Amcill-S, Pen A/N, Penbritin for injection, Polycillin for injection, Principen/N.*

Gentamicin sulfate—*Garamycin, Genoptic.*

References

1. Koblenzer PJ: Toxic epidermal necrolysis (TEN; Ritter's disease) and staphylococcal scalded skin syndrome. *Clin Pediatr* 15:724-730, 1976.

2. Elias PM, Fritsch P, Epstein EH Jr: Staphylococcal scalded skin syndrome. *Arch Dermatol* 113:207-219, 1977.

3. Lyell A: Toxic epidermal necrolysis (the scalded skin syndrome: The expanded clinical syndrome. *J Pediatr* 68:958-967, 1971.

4. Melish ME, Glasgow LA: Staphylococcal scalded skin syndrome: The expanded clincial syndrome. *J Pediatr* 68:958-967, 1971.

5. Sarai Y, Nakahara H, Ishikawa T, et al: A bacteriological study on children with staphylococcal toxic epidermal necrolysis in Japan. *Dermatologica* 154:161-167, 1977.

6. Melish ME, Glasgow LA: The staphylococcal scalded skin syndrome. *N Engl J Med* 282:1114-1119, 1970.

7. Rycheck RR, Taylor PM, Gezon HM: Epidemic staphylococcal pyoderma associated with Ritter's disease and the appearance of phage type 3B/71. *N Engl J Med* 269:332-337, 1963.

8. Lee HF, Wilson RB, Brown CD, et al: Impetigo and acute infectious exfoliative dermatitis of the newborn infant (Ritter's disease). *J Pediatr* 41:159-169, 1952.

9. Rasmussen JE: Toxic epidermal necrolysis. *Arch Dermatol* 111:1135-1139, 1975.

10. Kondo I, Sakurai S, Sarai Y: New type of exfoliatin obtained from staphylococcal strains, belonging to phage groups other than group II, isolated from patients with impetigo and Ritter's disease. *Infect Immunity* 10:851-861, 1974.

11. Kondo I, Sakurai S, Sarai Y, et al: Two serotypes of exfoliatin and their distribution in staphylococcal strains isolated from patients with scalded skin syndrome. *J Clin Microbiol* 1:397-400, 1975.

12. Rogolsky M, Warren R, Wiley BB, et al: Nature of the genetic determinant controlling exfoliative toxin production in *Staphylococcus aureus. J Bacteriol* 117:157-165, 1974.

13. Faden HS, Burke JP, Glasgow LA, et al: Nursery outbreak of scalded skin syndrome: Scarlatiniform rash due to phage group I *Staphylococcus aureus. Am J Dis Child* 130:265-268, 1976.

60 YEARS AGO IN THE AJDC

Pneumococcus Peritonitis in Infancy and Early Childhood

Reports of this disorder were the subject of six prior works dating from 1902 so that the entity was not new to observers. In thirteen years of experience at the Babies Hospital of New York, general peritonitis had been seen in 171 cases. Of these, nine had been demonstrated by culture to be due to the pneumococcus. Patients' ages ranged from 9 months to 4 years, the younger ages being more common because of the young age of the inpatient population.

Of the nine children, seven had a clearly demonstrated focus in the lung which antedated the development of peritoneal signs by as long as a month. There was fever in all; many had palpable abdominal masses and abdominal swelling. In one there was associated meningitis. The leukocyte count was elevated modestly with a prominence of polymorphonuclear forms. In two, the leukocyte count was over 25,000. In this group there was a single survivor.

In two children aged 2 and 2½, the mode of onset differed. There was high fever, vomiting, abdominal pain, and in one, diarrhea. No antecedent respiratory infections or symptoms had occurred. Both children were toxic, with tender and distended abdomens. In one leukopenia was noted; the leukocyte count in the other was 38,000 with 88 per cent. polymorphonuclear forms. One child had an exploratory laparotomy with findings of generalized peritonitis. Death ensued in both.

The pathogenesis of this condition has been debated. Some authorities feel the pneumococcus enters through the ear, others suspect the intestinal wall. The author agrees with most that this infection enters through the lung and that in certain cases the lung does not show any clear focus at all.

The treatment advised for penumococcal peritonitis is to keep the patient fully under the influence of morphia to keep the intestines at rest. Once localization of an abscess occurs, surgical drainage can be undertaken.—Paul W. Bearan, MD, Babies Hospital, New York (20:341-346, October 1920).

Cutaneous Necrosis Associated With Intravenous Nafcillin Therapy

Samuel J. Tilden, MD; J. Carl Craft, MD; Roberto Cano, MD; Robert S. Daum, MD, CM

• **Four children had cutaneous necrosis associated with the administration of intravenous (IV) nafcillin sodium therapy. One patient required skin grafting. Hospitalization was prolonged with this patient and with one other in an effort to ensure healing. Adult rats, inoculated subcutaneously with nafcillin that was appropriately diluted according to manufacturer's recommendations, exhibited similar lesions. Oxacillin sodium, methicillin sodium, and cephalothin sodium, similarly diluted, did not necrose skin. Nafcillin should be added to the list of agents that produce similar toxic conditions. Frequent observation of the IV infusion site to detect extravasation may obviate this hazard.**

(*Am J Dis Child* 134:1046-1048, 1980)

Nafcillin sodium is a semisynthetic, penicillinase-resistant penicillin, similar to oxacillin sodium and methicillin sodium in its antimicrobial spectrum. Intravenous (IV) therapy with nafcillin has been associated with several adverse reactions, including neutropenia, fever, rash, thrombophlebitis, and possibly nephropathy.[1-4] We have observed four patients with severe skin slough during IV nafcillin therapy; the purpose of this report is to alert clinicians to this hazard.

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REPORT OF CASES

CASE 1.—A 4-month-old female infant was admitted to Charity Hospital, New Orleans, in September 1978 for periorbital cellulitis. Initial therapy included IV nafcillin sodium (Unipen) at 150 mg/kg/day and chloramphenicol (Chloromycetin) sodium succinate at 80 mg/kg/day, each divided into four daily doses administered through a butterfly needle placed in a vein on the dorsum of the left hand. Nafcillin was administered intravenously over a period of 15 minutes after having been diluted in approximately 15 mL of 5% dextrose in water (final concentration, nafcillin sodium, 17.5 mg/mL diluent). Immediately after infusion, infiltration was observed; a small, nonerythematous, nontender vesicle surrounded the site. In the next six hours, this lesion progressed to a 3 × 1-cm area of discoloration. Progression to frank dermal necrosis with epidermal sloughing gradually developed over a four-day period. Treatment with sterile saline compress and application of sulfadiazine silver four times daily resulted in regression of the lesion, which was granulating well at the time of discharge from hospital on the 12th day. Nafcillin therapy was discontinued on the second hospital day after *Haemophilus influenzae* type B was grown in cultures of blood.

CASE 2.—A 9-day-old male infant was admitted to hospital in October 1978 for bullous impetigo. Aspiration of fluid from a bullous lesion revealed Gram-positive cocci with subsequent isolation of *Staphylococcus aureus*.

Initial therapy included IV nafcillin sodium at 200 mg/kg/day in four doses, which was administered in approximately 15 mL of 5% dextrose in water (final concentration, nafcillin sodium, 7 mg/mL diluent) via a butterfly needle placed in a scalp vein. On the sixth day of therapy, subcutaneous extravasation was noted after nafcillin infusion. Twenty-four hours later, the area of infiltration spread to involve a 5 × 5-cm area over the right frontoparietal region. This lesion was at first erythematous, became dusky, and showed frank necrosis at 48 hours. This process was severe, with bone visible in the depth of the wound (Fig 1). A right temporal transposition flap with split-thickness skin graft was required to cover the defect after debridement, and the patient was discharged without further complications on the 30th hospital day.

CASE 3.—A 7-week-old male infant was transferred to Tulane University Medical Center, New Orleans, for evaluation of facial cellulitis, bilateral otitis media, bilateral periorbital cellulitis, and a perforated nasal septum.

Initial antimicrobial therapy included IV nafcillin sodium (200 mg/kg/day in four doses) and gentamicin sulfate (7.5 mg/kg/day divided into three doses); slow resolution of the infected areas was noted. However, cellulitis over the nose and superior maxillary area persisted, and IV therapy was continued. On the 16th day, the IV solution (delivered from a 25-gauge butterfly needle) infiltrated into the dorsum of the right foot 1½ hours after nafcillin administration (in 15 mL of 5% dextrose

Fig 1.—Right frontoparietal cutaneous necrosis observed 24 hours after intravenous nafcillin sodium therapy. Patient required skin grafting (case 2).

in water; final concentration, nafcillin sodium, 10 mg/mL diluent). Over 48 hours, the skin became dusky, blue, and necrotic and sloughed over a 4 × 2-cm area; satellite blisters were present at the perimeter. Sulfadiazine silver cream was applied topically, and the patient was discharged one week later with the wound granulating well.

CASE 4.—A 3-month-old female infant was admitted to hospital for evaluation of congestive heart failure and pneumonia. Therapy included IV nafcillin sodium (200 mg/kg/day in four doses) and gentamicin sulfate (5 mg/kg/day in three doses). During transit to Charity Hospital, a dose of reconstituted nafcillin sodium (250 mg/mL) was given intravenously over a five-minute period via a 22-gauge IV catheter in the right antecubital fossa. No other medication was given in transit. On arrival, examination of the extremities revealed a 22-gauge catheter in the right antecubital vein surrounded by a 1.5-cm bulla.

The patient was treated for congestive heart failure, and the IV infusion site was changed. Bacitracin ointment was applied to the blistered area. However, no improvement was noted in the skin lesion ten days later when the infant died after cardiac surgery.

Effect of Subcutaneous Inoculation of Antibiotic Solutions on Skin

Drug, Concentration in mg/mL	Observed Skin Changes* Postinoculation Time, hr				
	2	12	24	48	96
Nafcillin sodium					
30	+	0	+	+ + +	+ + +
40	+	+ +	+ + +	+ + +	+ + +
250†	+ + +	+ + +	+ + + +	+ + + +	+ + + +
Methicillin sodium					
20	0	0	0	0	0
40	0	0	0	0	0
500†	+	+ + +	+ + + +	+ + + +	+ + + +
Oxacillin sodium					
20	0	0	0	0	0
40	0	0	0	0	0
167†	+	+	+ + +	+ + +	+ + +
Cephalothin sodium					
50	0	0	0	0	0
100	0	0	0	0	0
200†	+	0	0	+ +	0
5% dextrose in water	0	0	0	0	0

*Symbols are as follows: 0 indicates mild erythema or edema; + indicates mild induration, bluish discoloration; + + indicates thickened, dry skin; + + + indicates dark blue discoloration with depression of skin surface or frank dermal necrosis ≤5 mm in diameter; and + + + + indicates necrosis >5 mm.

†Concentration in vial when reconstituted.

ANIMAL STUDIES

Adult Sprague-Dawley outbred albino rats were inoculated with nafcillin, oxacillin, methicillin, cephalothin sodium, or 5% dextrose in water. All antimicrobial solutions were freshly prepared by reconstitution with sterile water or 5% dextrose in water according to the manufacturer's recommendation. Further dilution in 5% dextrose in water yielded solutions appropriate for direct IV instillation (Table). The hair over the abdomen was trimmed with an electric shaver, and 0.2 mL of a test solution was inoculated subcutaneously. The skin over the inoculation site was inspected by a blinded observer 2, 12, 24, 48, and 96 hours after inoculation; all solutions were evaluated in duplicate.

RESULTS

The results are summarized in the Table. Undiluted methicillin and nafcillin produced severe necrosis 24 hours after inoculation. Necrosis with high-concentration oxacillin was less severe; cephalothin did not necrose the overlying skin. When diluted to concentrations recommended by manufacturers for IV infusion,[5] only nafcillin produced necrosis (Fig 2). No skin changes were observed after inoculation with 5% dextrose in water.

COMMENT

Intravenous nafcillin therapy has been associated with minimally toxic conditions in pediatric patients. Feldman et al[6] reported phlebitis in one of 46 patients, transient neutropenia in two of 30, and mild elevation of SGOT levels in three of 27 patients treated with nafcillin for presumed or proven staphylococcal infection. Arbeter et al,[3] in a double-blind comparison of nafcillin and oxacillin therapy, observed thrombophlebitis in 17 of 52 patients who were receiving nafcillin; 14 of 17 were 10 years of age or older. By contrast, thrombophlebitis developed in only four of 62 patients who were treated with oxacillin. Elevated SGPT concentrations occurred in 13 of 62 patients receiving oxacillin and in six of 52 patients receiving nafcillin.

We observed four infants, aged 9 days to 4 months, who had cutaneous necrosis associated with the administration of IV nafcillin. The technique of nafcillin administration was reviewed with the appropriate nursing personnel; in each case, patency of the IV line was established prior to nafcillin administration. As per the manufacturer's recommendation,[5] nafcillin sodium was first reconstituted to a concentration of 250 mg/mL with sterile water. With the exception of patient 4, it was next diluted in 15 to 20 mL of 5% dextrose in water and administered over a period of 15 to 30

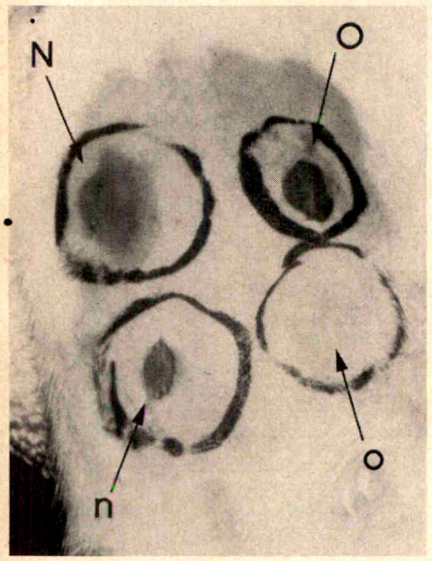

Fig 2.—Cutaneous necrosis after subcutaneous injection of 0.2 mL of nafcillin sodium or oxacillin sodium. N indicates nafcillin sodium, 250 mg/mL; n, nafcillin sodium, 40 mg/mL; O, oxacillin sodium, 167 mg/mL; o, oxacillin sodium, 40 mg/mL.

minutes. At least two different lots of nafcillin were used in our patients. Treatment of the necrotic area consisted of local care except in one patient who required skin grafting; in two patients, hospitalization was prolonged because of the severity of their lesions.

Other agents have been associated with cutaneous necrosis after IV extravasation. Doxorubicin, mechlorethamine hydrochloride, mitomycin, vincristine, calcium salts, norepinephrine, sodium bicarbonate, radiopaque contrast material, methylene blue, and 10% dextrose in water have all been implicated in this regard.[7-12] None of the aforementioned agents were administered to any of our patients.

Experimental subcutaneous inoculation of adult rats with nafcillin produced lesions similar to those observed in our patients. Dermal necrosis was not observed after methicillin, oxacillin, and cephalothin inoculation.

Since the occurrence of these cases, we have emphasized the importance of careful dilution of nafcillin prior to administration and frequent observation of the IV infusion site, with prompt discontinuation of therapy if any suggestion of infiltration is present. These precautions may help to minimize cutaneous necrosis but may not be fully preventive. Physicians who choose IV nafcillin therapy for their patients should be aware of cutaneous necrosis as a hazardous complication of therapy.

Wesley Galen, MD, reviewed the manuscript. John Willard and Barbara Palmisano, MD, assisted with the rat experiments. Kathleen Kustudich provided secretarial support.

Nonproprietary Names and Trademarks of Drugs

Cephalothin sodium—*Keflin.*
Gentamicin sulfate—*Garamycin, Genoptic.*
Sulfadiazine silver—*CF-100, Silvadene.*

References

1. Kancir LM, Tuazon CU, Cardella TA, et al: Adverse reactions to methicillin and nafcillin during treatment of serious *Staphylococcus aureus* infections. *Arch Intern Med* 138:909-911, 1978.
2. Greene GR, Cohen E: Nafcillin-induced neutropenia in children. *Pediatrics* 61:94-97, 1978.
3. Arbeter AM, Tolpin MD, Piercy SA, et al: Nafcillin-oxacillin comparative clinical trial, abstracted. *Pediatr Res* 12:489, 1978.
4. Parry MF, Ball WD, Conte JE, et al: Nafcillin nephritis, letter to the editor. *JAMA* 225:178, 1973.
5. *Physicians' Desk Reference.* Oradell, NJ, Medical Economics Co, 1979, pp 715-717, 720-721, 1031-1033, 1890-1892.
6. Feldman WE, Nelson JD, Stanberry LR: Clinical and pharmacokinetic evaluation of nafcillin in infants and children. *J Pediatr* 93:1029-1033, 1978.
7. Bowers DG Jr, Lynch JB: Adriamycin extravasation. *Plast Reconstr Surg* 61:86-92, 1978.
8. Grech P, Spitz L: Fetal complications of amniography. *Br J Radiol* 50:110-112, 1977.
9. Jackson IT, Robinson DW: Severe tissue damage following accidental subcutaneous infusion of bicarbonate solution. *Scott Med J* 21:200-201, 1976.
10. Perry PM, Meinhard E: Necrotic subcutaneous abscesses following injections of methylene blue. *Br J Clin Pract* 28:289-291, 1974.
11. Yosowitz P, Ekland DA, Shaw RC, et al: Peripheral intravenous infiltration necrosis. *Ann Surg* 182:553-556, 1975.
12. Gylling U, Rintala A: Treatment of noradrenaline infusion necrosis. *Ann Chir Gynaecol Fenniae* 55:271-275, 1966.

Early Growth Patterns of Methadone-Addicted Infants

Ira J. Chasnoff, MD; Roger Hatcher, PhD; William J. Burns, PhD

• **The early growth patterns of 15 full-term infants born to mothers on well-controlled, low-dose methadone hydrochloride maintenance were studied. Mean birth weight and length were at the tenth percentile, and mean head circumference was at the fifth percentile. Early withdrawal symptoms persisted for three to four months, and mean growth parameters continued along their respective percentiles. As withdrawal symptoms abated at 4 to 6 months, infants became more responsive, easier to handle, and demonstrated an accelerated growth pattern. This acceleration of growth at 4 to 6 months of age corresponded to patterns found in previous animal studies.**

(*Am J Dis Child* 134:1049-1051, 1980)

Though the literature has had very little information on the methadone hydrochloride-addicted neonate, there now is evidence that the early symptoms described in the neonatal addict continue in attenuated or subacute form throughout early infancy.[1-3] Restlessness, hyperactivity, brief sleep, and colic and feeding problems reportedly continue for the first two to three months. At approximately 4 to 6 months, however, the infants become more responsive and easier to handle and demonstrate catch-up developmental growth. At present, there is no longitudinal information regarding the somatic growth of methadone-addicted newborns during this period. This study reports the early growth patterns of infants born to mothers on low-dose methadone maintenance.

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PATIENTS AND METHODS

Fifteen infants born during 1978 to mothers on a well-controlled, low-dose methadone maintenance program at Prentice Women's Hospital and Maternity Center, Chicago, were studied prospectively. All of the women had conceived while taking heroin and joined the methadone maintenance program in the first or early second trimester of pregnancy. Maternal urine samples were obtained daily in order to screen for illicit drug use. Intensive prenatal care was provided for each woman, and, in addition, each prospective mother received individual counseling and family therapy. Eighteen women were enrolled in the program during the one-year period. Three were disqualified because of continued use of illicit drugs or were lost to follow-up during pregnancy.

The mean age of the 15 women was 23.5 ± 4.5 years. The racial identities and socioeconomic classes of the study group closely reflected the general population of the hospital. The pregnancies were uncomplicated except for one woman with gestational diabetes and four women with a positive VDRL at delivery. One woman required a cesarean section due to cephalopelvic disproportion.

Maternal weights prior to pregnancy as reported by the women, ranged from 42.7 to 75 kg. Among the study population, seven of the women were primagravidas, and six had had more than four pregnancies. There was a history of 22 previous abortions, half of which were spontaneous. Five women did not smoke tobacco, eight smoked less than or up to one pack of cigarettes per day, and two women smoked more than one pack per day.

The initial daily dosage of methadone varied among the women, but the dosage was steadily decreased to the lowest level that would prevent craving or withdrawal in the mother. By the beginning of the third trimester, each woman was on a maintenance dose of methadone. Four women received 5 mg of methadone hydrochloride daily; three women received 10 mg daily; five women received 15 mg daily; two women received 20 mg daily; and one woman received 40 mg daily. These dosages were held at the same level for the remainder of the pregnancy. No woman was completely detoxified during pregnancy. Daily methadone dosage did not vary during labor, delivery, or in the postpartum period.

Some of the maternal variables that might affect infant birth weight, eg, race, cigarette smoking, and daily and total methadone dose, were statistically analyzed. The relationships between each of these maternal variables and neonatal birth weight was assessed by χ^2 analysis.

Infants were followed up from birth and received routine well-child care by the attending pediatrician, first at weekly, and later at monthly, appointments. Each infant was observed for signs of methadone withdrawal. Weight, crown-to-heel length, and frontooccipital head circumference were recorded at each visit. Twice-weekly observations in the home regarding mother-infant interaction, infant behavior, irritability, feeding problems, and sleep patterns were recorded by a visiting nurse.

All infants were fed a standard commercial formula with iron, and solid feedings were begun at 6 months of age. Feeding history was obtained from the mothers and documented through records of home visits made by a visiting nurse. All infants received a minimum of 120 calories/kg/day throughout the study. Mothers were questioned specifically about infant behavior, irritability, feeding problems, and sleep patterns at home. All mothers underwent continuous individual counseling as well as family therapy throughout the period of follow-up with the infants.

The conditions of 11 of the infants were evaluated with the Brazelton Neonatal Behavorial Assessment Scale.[4] Four infants were discharged prior to testing. The scale was administered in a quiet room after 2 days of age by experienced examiners who had demonstrated reliability in the use of this examination. The Bayley Scale of Development[5] was administered to 12 infants at 3 months of age and again to six of these infants at 6 months.

RESULTS

General

All 15 newborns were of singleton birth at term (38 to 42 weeks) gesta-

tion as ascertained by the criteria of Ballard et al.[6] One infant had meconium staining of the amniotic fluid at delivery. The mean Apgar score at one minute was 8.1 (SD, 0.24) with one infant having a score below 7. At five minutes, the mean Apgar score was 8.6 (SD, 0.14) with all scores being 7 or above. One infant had a second-degree hypospadias; no other congenital malformations were present. No infant born to a mother with positive VDRL during pregnancy had serologic evidence of congenital syphilis.

Psychomotor Development

All 15 infants demonstrated some degree of withdrawal symptoms beginning on the second to fourth day of life. Ten infants demonstrated mild jitteriness and irritability with no progression of symptoms. Four infants demonstrated these same symptoms but to a degree that interfered with feedings and that required therapy. One infant had a generalized seizure on the third day of life. All five infants who required therapy were treated with phenobarbital, 8 to 15 mg/kg/day, and no longer received medication by 6 weeks of age.

On evaluation of the infants' conditions with the Brazelton Newborn Assessment Scale, reflexes, muscle tone and movement, and orientation responses were found to be normal. There were 11 instances of poor habituation to light and sound stimulation; eight, of rapid build-up to crying states; nine, of irritability; nine, of insulated crying states, in which the infant was inconsolable; seven, of labile state control; and nine, of predominant fussing and crying states.

Through the age of 3 to 4 months, an infant's sleep problems, hyperactivity, irritability, and feeding difficulties were reported by parents and visiting nurses. Examination of the infants by the pediatrician through this age revealed irritable infants with hypertonia and hyperreflexia. Beginning at 3 to 4 months of age, many of the symptoms and signs began to resolve, and the infants became more responsive and easier to handle. By 6 months of age, very few, if any, behavioral problems were reported by parents and nurses.

On the Bayley Scale of Development, the means of the Mental (MDI) and Motor (PDI) Indices were in the average range when infants were 3 months of age (where the mean MDI and PDI scores for the general population were 100; SD, 16). Of 12 infants tested, the mean MDI score was 103 (SD, 11.6), and the mean PDI score was 112 (SD, 14.2). At 6 months of age, there was a downward deflection of 11 and 19 points on the MDI and PDI, respectively (SD, 6 and 14.3, respectively). However, the six-month scores were within the normal range, though near the lower limit.

Growth

The mean birth weight, 2,957 g (range 2,540 to 3,742 g; SD, 349 g), of the study infants was not significantly different from the mean birth weight (3,340 g) of the general newborn population in our hospital. Using χ^2 analysis, no statistically significant relationship was found between birth weight of the study infants and racial group or between birth weight and daily or total maternal methadone dose. Though the two largest infants were born to mothers who did not smoke, there was no significant relationship between birth weight and smoking.

The mean birth weight of the male and of the female infants was plotted on a growth chart appropriate for sex constructed by the National Center for Health Statistics.[7] These charts are based on measurements of infants in the general US population.

For simplicity, the charts in Fig 1 to 3 are adapted from graphs of male and female infants so that the normal percentiles drawn in the illustrations serve for both male and female infants. The same growth patterns resulted when the mean measurements for each sex were recorded on sex-appropriate graphs.

The mean birth weight for the methadone-addicted infants fell at the tenth percentile (Fig 1). The subsequent mean weights with SDs also were plotted on the growth chart. The mean weight remained at the tenth percentile until 4 months of age, when the mean weight of the study infants began crossing the percentiles. By 7½ months of age, the mean weight of the study infants lay near the 40th percentile.

Monthly measurements of infant length demonstrated a similar pattern (Fig 2). The initial mean length of 48.4 cm (range, 46 to 52 cm; SD, 1.6 cm) lay at the tenth percentile, and subsequent mean lengths remained at this level until 4 months of age. By 7½ months, mean length for the study infants lay between the 25th and 50th percentiles. Perhaps more importantly, the mean head circumference at birth of 32.9 cm (range, 31 to 35 cm; SD, 0.01 cm) lay at the fifth percentile (Fig 3) and followed this percentile curve until infants were 4 months old, when the mean increased to the tenth percentile. By 7½ months, the infants' mean head circumference approached the 25th percentile.

COMMENT

Early withdrawal symptoms of irritability, sleep problems, hyperactivity, feeding difficulties, and hypertonia persisted for three to six months. All infants had adequate caloric intake for growth during this time, as demonstrated by the fact that weight, length, and head circumference growth were maintained at a normal rate along the fifth to tenth percentile. As withdrawal symptoms abated at 4 to 6 months of age, infants became more responsive, easier to handle, and showed an accelerated growth pattern.

This early depression of growth could be due to the direct effect of methadone on the hypothalamic-hypophyseal axis of the newborn.[8] There are many reported effects of opiates referable to the hypothalamus,[9-11] and rapid loss of body weight has been demonstrated in adult rats chronically treated with morphine.[9]

Animal studies by Friedler and Cochin have demonstrated the direct action of maternal opiates on the growth of newborn rats.[8] Rats born to mothers who had been treated prenatally with morphine had a significant depression of body weight compared with a control population. At birth, the size and weight of the experimental and control litters were similar; however, the offspring born to the mor-

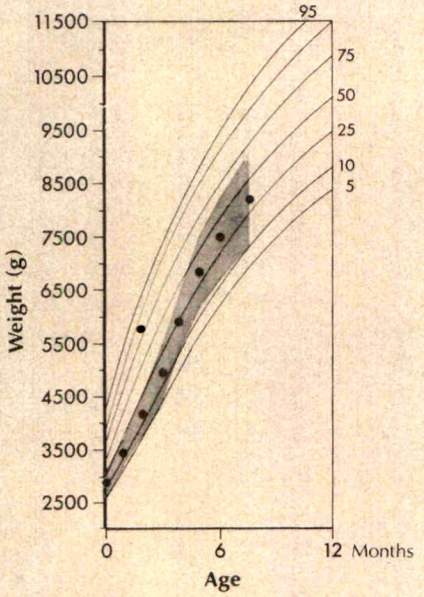

Fig 1.—Mean weights of study infants (N = 15) by age. Shaded areas depict ± 2 SD. For source of normal percentiles, see text.

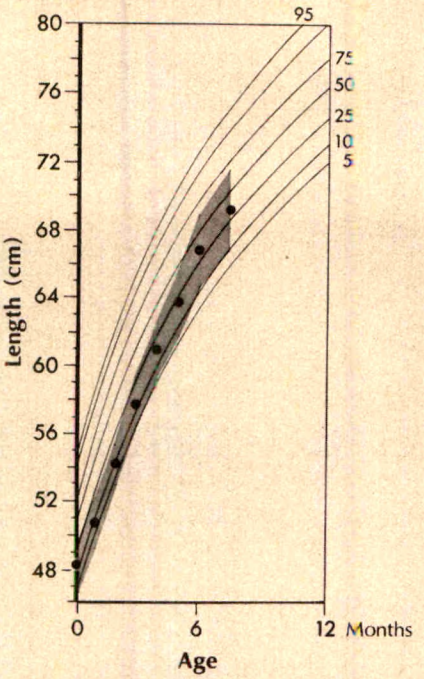

Fig 2.—Mean lengths of study infants (N = 15) by age. Shaded area depicts ± 2 SD. For source of normal percentiles, see text.

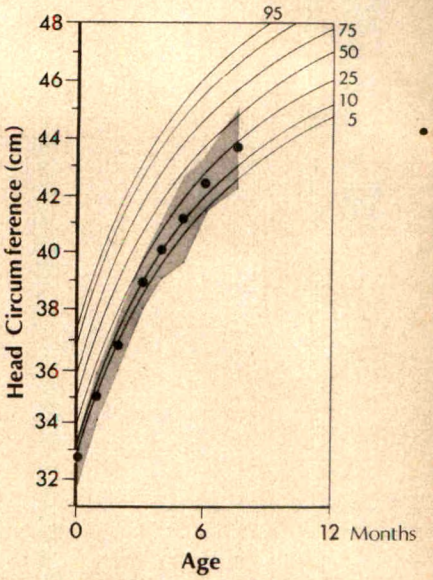

Fig 3.—Mean head circumference of study infants (N = 15) by age. Shaded area depicts ± 2 SD. For source of normal percentiles, see text.

phine-treated mothers showed a depressed rate of growth commencing at 4 weeks of age. Growth recovery then occurred, and the somatic growth of the experimental rats returned to control levels by 2 months of age.

In the newborn infant, 85% of methadone is protein bound and is converted to an active metabolite before being slowly excreted by the liver.[12] The neonatal tissues serve as a "reservoir of the drug,"[13] and the methadone exerts a persistent effect on the infant. We would postulate that, as the drug is excreted by the infant, plasma and tissue drug levels fall, the endocrinological effect of the drug subsides, and growth recovers.

Many factors influence growth, and the acceleration of growth at 4 months of age demonstrated by the infants in this study could be the result of many interacting variables, including alterations in maternal-infant interaction and nutrition. However, the data presented here do correspond to information obtained from previous animal studies and may provide valuable insight into the fundamental effects of methadone on the early growth patterns of infants born to mothers on low-dose methadone maintenance. Though the infants demonstrate an acceleration of physical growth between 4 and 6 months of age, there is no similar acceleration in their mental or motor development. In fact, there is some suggestion of a mild deceleration in psychomotor development during this period. Long-term observation and follow-up will be necessary in order to determine if these alterations in the physical and mental development of methadone-addicted infants are transitory or have more lasting implications.

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Gay Diggs, RN, Judith Adler, MSW, and Laura Kostro helped in the completion of this study.

References

1. Lipsitz PJ, Blatman S: Newborn infants of mothers on methadone maintenance. *NY State J Med* 74:994-999, 1974.

2. Ramer CM, Lodge A: Neonatal addiction: A two year study. Part I: Clinical and developmental characteristics of infants of mothers on methadone maintenance. *Addict Dis* 2:227-234, 1975.

3. Wilson GS, Desmond MM, Verniaud WM: Early development of infants of heroin-addicted mothers. *Am J Dis Child* 126:457-462, 1973.

4. Brazelton TB: *Neonatal Behavioral Assessment Scale*. Philadelphia, Spastics International Medical Publications, 1976, pp 63-64.

5. Bayley N: *Manual for the Bayley Scales of Infant Development*. New York, Psychological Corp, 1969, pp 40-98.

6. Ballard JL, Kazmaier K, Driver M: A simplified assessment of gestational age. *Pediatr Res* 11:374, 1977.

7. National Center for Health Statistics Growth Charts, in *Monthly Vital Statistics Report*. Rockville, Md, Health Resources Administration, June 1976, vol 25, No. 3, suppl (HRA) 76-1120.

8. Friedler G, Cochin J: Growth retardation in offspring of female rats treated with morphine prior to conception. *Science* 175:654-656, 1972.

9. Barraclough CA, Sawyer CH: Inhibition of the release of pituitary ovulatory hormone in the rat by morphine. *Endocrinology* 57:329-337, 1955.

10. George R, Way EL: The role of the hypothalamus in pituitary-adrenal activity and antidiuresis by morphine. *J Pharmacol Exp Ther* 125:111-115, 1959.

11. George R, Lomax P: The effects of morphine, chlorpromazine, and reserpine on pituitary-thyroid activity in rats. *J Pharmacol Exp Ther* 150:129-134, 1965.

12. Way EL, Adler TK: The pharmacologic implications of the fate of morphine and its surrogates. *Pharmacol Rev* 12:383-446, 1960.

13. Dole VP, Kreek MJ: Methadone plasma level: Sustained by a reservoir of drug in tissue. *Proc Natl Acad Sci USA* 70:10, 1973.

Anaerobic Bacteremia in Children

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• Twenty-nine anaerobic isolates were recovered from 28 pediatric patients with anaerobic bacteremia: 14 *Bacteroides* sp (11 in the *B fragilis* group); four anaerobic Gram-positive cocci; four *Clostridium* sp; four *Propionibacterium acnes*; and three *Fusobacterium* sp. No aerobic bacteria were isolated from these patients. The gastrointestinal tract was the possible portal of entry in 13 instances, eight of which were due to *Bacteroides* organisms, four to *Clostridium* sp, and one to *F nucleatum*. The ear, sinus, and oropharynx were probable portals of entry in seven instances, four of which were due to *Peptococcus* sp and two to *Fusobacterium* sp. Five patients (18%) died; four had bacteremia caused by *B fragilis* group, and one had bacteremia caused by *P acnes*. The average duration of antimicrobial therapy was 20 days (range, seven to 72 days). The early recognition and rapid institution of appropriate antimicrobial and surgical therapy are of utmost importance in improving the outcome of these patients.

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Anaerobic organisms have been rarely isolated from blood cultures of pediatric patients. These microbes represent a small percentage of the total number of positive blood cultures recovered from children. This may be due partly to the difficulty in isolating and identifying these organisms. There is, however, a growing awareness of the role of anaerobic organisms in pediatric infection, including bacteremia.[1-5]

This communication presents the combined experiences of two medical institutions in the isolation of anaerobic microorganisms from blood cultures obtained from infants and children. The clinical data were reviewed and correlated with the bacteriological findings, and only cases of patients with clinical bacteremia are reported. Included are neonatal bacteremia, bacteremia associated with underlying disease and with artificial devices (neurological and cardiovascular shunts), and bacteremia in normal subjects.

MATERIALS AND METHODS

Medical records of all children with anaerobic bacteremia who were hospitalized between Jan 1, 1974, and March 1, 1975, at UCLA Medical Center, and between Jan 1, 1976, and March 31, 1980, at Children's Hospital National Medical Center (CHNMC), Washington, DC, were reviewed retrospectively. The diagnosis of anaerobic bacteremia was made when anaerobic bacteria were isolated from blood cultures and their recovery correlated with the clinical findings.

All blood cultures were inoculated at the patient's bedside into 50 mL of trypticase soy broth containing 0.03% sodium polyanetholesulfonate at UCLA Medical Center, or into trypticase soy broth containing 0.05% sodium polyanetholesulfonate at CHNMC. They were incubated at 35 °C for a period of seven days (UCLA) or ten days (CHNMC). All bottles were inspected daily for evidence of macroscopic growth. In addition, a blind subculture of macroscopically negative bottles was done at 24 and 48 hours. Approximately 0.1 mL of broth from each bottle was inoculated onto two chocolate agar plates and incubated at 35 °C in 7% CO_2 and in an anaerobic jar. All plates were examined for growth at 24 and 48 hours. All macroscopically positive blood cultures were subcultured to appropriate plating media as determined by Gram-stain characteristics. The anaerobic jar sys-

Organism	No. of Cases
Peptococcus sp	3
Propionibacterium acnes	4
Clostridum sp	4
Bacteroides sp	3
Bacteroides fragilis group	11
Fusobacterium† *nucleatum*	3

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tem was used for incubation of subcultures from bottles suspected of containing anaerobes and for most biochemical tests. Anaerobic plating media were preincubated for 48 hours under an atmosphere of CO_2 as described previously.[6] Biochemical identification of anaerobic strains was done by methods previously described.[6,7] Gas chromatography of metabolic end products was done by the methods of Holdeman and Moore.[8]

RESULTS

The clinical and bacteriological data of 28 pediatric patients with anaerobic bacteremia are presented in Table 1. There were 16 males and 12 females with an age span from 2 days to 14 years (average, 7 years 4 months). The Figure shows the distribution of anaerobic bacteria isolated as a function of age. The duration of symptoms prior to therapy was one to 23 days (average, 6.6 days).

Twenty-nine anaerobic isolates were recovered from the 28 patients. No aerobic bacteria were isolated from these patients. In descending frequency, organisms isolated were as follows: *Bacteroides* sp in 14 patients (11 in the *B fragilis* group); Gram-positive anaerobic cocci in four; *Propionibacterium acnes* in four; *Clostridium* sp in four; and *Fusobacterium* sp in three (Table 2).

Source of Entry

The probable portals of entry for the blood culture isolates are given in Table 2. The gastrointestinal (GI) tract predominated (13 cases), followed by the respiratory tract (ear, sinus, and oropharynx, seven); the lower respiratory tract (three); cardiovascular shunts and neurological shunts (three); and skin and soft tissue (three). When the GI tract was the probable portal of entry, *Bacteroides* sp (eight isolates, including five of the *B fragilis* group) and *Clostridium* sp (four isolates) were the organisms most frequently recovered from blood. The predominant anaerobic organisms recovered in association with infections of the ear, sinus, and oropharynx were *Peptococcus* sp (in four cases) and *F nucleatum* (in two cases). *Propionibacterium acnes* was grown in cultures taken from four patients, three of whom had artificial cardiac valves or ventriculoatrial shunts. Two of these patients also were initially observed to have meningitis caused by a similar organism. All lower respiratory tract infections that served as a probable source of bacteremia were due to isolates belonging to the *B fragilis* group.

No obvious focus of infection was noted in six patients; however, it is of interest that all of these patients had some GI problem that might have served as a source of the bacteremia. Of further interest is that four of these patients had bacteremia caused by *Clostridium* sp.

Extravascular Infection

Anaerobic organisms recovered from blood were also isolated from other infected sites in 16 (57%) of the patients. In eight of the 16 patients, anaerobic bacteria were mixed with other anaerobic and/or with aerobic organisms (two to five bacteria per specimen of pus). Extravascular sites from which anaerobic organisms were recovered included the following: abscesses, four cases; CSF, three; peritoneal fluid, four; tracheopulmonary aspiration, two; sinuses, two; and sinus and subdural empyema, one. Seven of the eight children who had soft-tissue abscesses or local collections of pus required surgical drainage. Some of these patients had recurrent or persistent bacteremia until proper surgical drainage was performed. Four patients also had extravascular collections of pus; however, anaerobic organisms were not recovered from these sites either because anaerobic cultures were not obtained or because the specimens were inappropriately transported.

e 1.—Clinical Data on 28 Patients With Bacteremia due to Anaerobic Bacteria

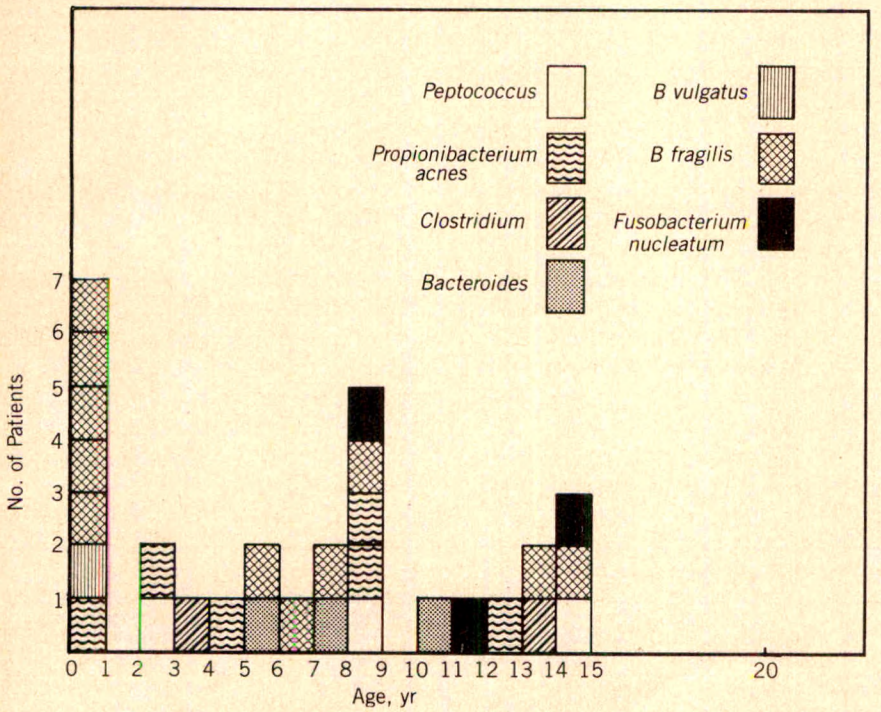
Probable Source	Underlying Conditions	Other Complications	Antimicrobial Therapy	Results	Other Infectious Sites With Similar Bacteria
Abscesses (2),* sinusitis (1)	None (3)	Subdural empyema (1); meningitis (1)	Penicillin G potassium (1); ampicillin sodium (1); oxacillin sodium (1)	Cured (3)	Subdural empyema and sinus (1); abscess (1)
Cardiovascular shunts (3); periorbital cellulitis (1)	Hydrocephalus (1)	Meningitis (2)	Penicillin (2); methicillin (1); ampicillin (1)	Cured (3); died (1)	CSF (2)
Gastrointestinal (GI) tract (4)	Sickle cell disease (2)	None (4)	Penicillin (2); ampicillin (2)	Cured (4)	None (4)
Perforation viscus (2); ileus (1)	Acute lymphocytic leukemia (1)	Peritonitis (1)	Clindamycin hydrochloride (2); carbenicillin disodium (1)	Cured (3)	Peritoneal fluid (2)
Perforated appendix (3); pneumonia (3); abscesses (3); GI tract (1); necrotizing enterocolitis (1)	Mental retardation (2); acute lymphocytic leukemia (1); selective IgG deficiency (1); prematurity (1); recent hip surgery (1)	Meningitis (2); peritonitis (2); septic shock (1); empyema (1)	Clindamycin (6); penicillin (3); chloramphenicol sodium succinate (2); ampicillin (2); carbenicillin (1)	Cured (7); died (4)	Abscess (3); tracheopulmonary aspiration (2); peritoneal fluid (2); CSF (1)
Sinusitis (2); perforated appendix (1)	Chronic otitis media (1)	Subdural empyema (1); periorbital cellulitis (1)	Chloramphenicol (2); clindamycin (1)	Cured (3)	Sinuses (2)

*Number of cases in parentheses.
†In one case, *Peptococcus* sp was also recovered in the blood culture.

Antimicrobial Therapeutics

Penicillins (except carbenicillin disodium) were used in the treatment of 16 patients; clindamycin hydrochloride, in nine; chloramphenicol sodium succinate, in four; and carbenicillin, in two. Twelve patients received a combination of two or three of these antibiotics for treatment of organisms present at other infection sites. The average duration of therapy in the patients who recovered was 20 days (range, seven to 72 days), and the duration of therapy was related to the presence and severity of other infectious sites and complications (Table 2). Therapy was longest in the treatment of meningitis, wound, abscess, sinusitis, and empyema.

Bacteriological cure of the bacteremia occurred in 23 patients. Of the five children who died, three died within four days after therapy was instituted. Two of these were newborns. One child had bacteremia and meningitis caused by *P acnes*. The second, a newborn with anaerobic bacteremia, also had meningitis and perinatal pneumonia. *Bacteroides vulgatus* was isolated from both sites and the blood culture. Because of a delay in the identification of this organism, the child was inappropriately treated. A third patient, a 6-year-old suffering from acute lymphocytic leukemia, had a perirectal abscess and died in spite of vigorous antimicrobial therapy and drainage of the abscess. The fourth child, a 5-year-old who had a selective IgG 2 deficiency and severe anoxic brain damage, had bronchopneumonia and sepsis due to *B fragilis*. The fifth child who died, a premature newborn, suffered from necrotizing enterocolitis, perforation of the colon, and sepsis due to *B fragilis*.



Age distribution of patients with anaerobic bacteremia.

Table 2.—Probable Sites of Source of Bacteremia

Bacteria	Ear, Sinus, Oropharynx	Skin, Soft Tissue	Shunts	Gastrointestinal Tract	Lower Respiratory Tract	Total
Peptococcus sp	4†					4
Propionibacterium acnes	1		3			4
Clostridium sp				4		4
Bacteroides sp				3		3
B vulgatus					1	1
B fragilis		3		5	2	10
Fusobacterium nucleatum	2†			1		3
Total	**7**	**3**	**3**	**13**	**3**	**29†**

*According to number of cases of anaerobic bacteria.
†One case represents a mixed infection with *Peptococcus* sp and *F nucleatum*.

Meningitis

In five (18%) of the children, meningitis occurred that was associated with *B fragilis* (two cases), *P acnes* (two), and *Peptococcus* sp (one). A direct extension of the organism from an infection site to the meninges might have occurred in two of these children, both of whom had surgical drainage of their local collection of pus. One of these patients had pansinusitis and required a Caldwell-Luc procedure, where a direct extension of the inflammation to the subdural space through the cribriform plate was demonstrated. Ethmoid drainage and frontal craniotomy yielded pus from the sinus as well as the subdural space. The child with pilonidal sinus had surgical drainage and subsequent removal of the sinus tract.

COMMENT

Anaerobic bacteremia has rarely been described in pediatric patients.[9,10] In one study, anaerobic organisms were recovered in six of 34 children who required general anesthesia and nasotracheal intubation for dental repair.[11] Another study documented bacteremia in 28 children who were undergoing dental manipulations.[12] Among the 28 isolates recovered, 21 were anaerobes (*Propionibacterium* sp, nine; *Veillonella alcalescens*, five; *B melaninogenicus*, three; *Peptostreptococcus* sp, two; and *Eubacterium* sp and *Fusobacterium* sp, one each).

In a survey of anaerobic infections in children, blood cultures have been found to be the second most frequent source of anaerobic organisms.[1] The

predominant isolate from blood cultures (56% to 65%) is *P acnes*,[1,2] a normal inhabitant of the skin. Many of these isolates may reflect contamination of the blood cultures by the skin flora; however, *P acnes* can cause bacteremia, especially in association with shunt infections.[13] All of the patients with *P acnes* bacteremia included in our study had clinical infection and all but one responded to antimicrobial therapy. Furthermore, two of them had meningitis caused by this organism after installation of cardiovascular shunts. The possibility that some of the other isolates recovered from our patients were contaminates is unlikely. The high incidence of recovery of similar bacteria from extravascular sites, the lack of recovery of aerobic isolates, and the response to therapy support this contention.

Bacteroides fragilis, anaerobic Gram-positive cocci, and *Fusobacterium* sp were the other anaerobic organisms most commonly isolated from blood cultures in three recent studies.[1-3] Most of the patients described in these studies were over 6 weeks of age and suffered from chronic debiliating disorders such as malignant neoplasms, immunodeficiencies, or chronic renal insufficiency, along with long-term prognosis. *Bacteroides* sp were also isolated frequently after perforation of viscus and appendicitis.[14,15]

Neonatal Bacteremia

A recent report[4] described anaerobic bacteremia in 23 newborns and reviewed 57 additional cases from the literature. The yield of anaerobic bacteria in 23 newborns seen over a period of 3.5 years represented 1.8 cases per 1,000 live births and accounted for 26% of all instances of neonatal bacteremia at that hospital. The bacteremia episodes were associated with prolonged labor, premature rupture of membranes, maternal amnionitis, prematurity, fetal distress, and respiratory difficulty. In that series, the patients with neonatal anaerobic bacteremia had better prognoses than did newborns with bacteremia caused by facultative bacteria. Only one patient of the 23 (4%) died; however, the mortality from the cases of anaerobic bacteremia reviewed from the literature was 26%. Neonatal sepsis due to facultative organisms has been reported to range from 30% to 44%.[16,17]

The isolation of nonhistotoxic *Clostridium* sp from 18 newborns with bacteremia has been described.[18] Bacteremia was also found to be associated with necrotizing enterocolitis of the newborn. *Clostridium butyricum* was recently isolated from blood cultures obtained from 12 newborns with that disease.[19]

Bacteremia in newborns has also been attributed to *Bacteroides* sp[20-22] and *F nucleatum*,[23] organisms that can be acquired during the infant's passage through the birth canal. Moreover, six episodes of *B fragilis* bacteremia associated with perinatal pneumonia were reported recently.[1,24] The two newborns in our series died within four days of therapy. These patients were infected by organisms of the *B fragilis* group and received inappropriate antimicrobial therapy. Though the occurrence of bacteremia in newborns is infrequent, our experience indicates the need for proper antibiotic coverage of the newborn against *B fragilis*.

Predisposing Factors

Predisposing factors to anaerobic bacteremia in adults include malignant neoplasms,[25,26] hematologic disorders,[27] transplantation of organs,[28] recent GI or obstetrical gynecological surgery,[26,27,29] intestinal obstruction,[30] diabetes mellitus,[26] postsplenectomy,[28] use of cytotoxic agents or corticosteroids,[26] and use of prophylactic antimicrobial agents for "bowel preparation" prior to surgery.[26,29]

Predisposing conditions were also noted in our patients. Two had malignant neoplasms, two suffered from hematologic abnormalities, and one had an immune deficiency. It is of interest that 82% of the bacteremias in our series of patients occurred in children who had no immunosuppression or malignant neoplasms, in contrast to another study[10] where anaerobic bacteremia occurred more frequently in children with these predisposing factors.

As reported in adults, the strain of anaerobic organisms recovered depended to a large extent on the portal of entry and the underlying disease.[9] Our findings support previous studies of adults[31] and children[10] that report that *Bacteroides* sp, including the *B fragilis* group, were the predominant isolates from patients in whom the GI tract was the probable portal of entry. As previously reported in adults,[32] we found the ear, sinus, and oropharynx as possible portals of entry that predisposed patients to bacteremia with *Peptococcus* sp and *Fusobacterium* sp. This is not surprising since these organisms are part of the normal flora of such anatomical sites and can be involved in local infections.[9]

Pneumonia occurred in three of our patients subsequent to bacteremia with organisms belonging to the *B fragilis* group. This has also been noted in adults[33] and newborns.[4] Though *Bacteroides* accounted for the majority of the episodes of bacteremia in our study, other studies have shown relatively infrequent isolation of these organisms in children[33] except during the neonatal period.[4]

The clinical features of anaerobic bacteremia in our patients were not much different from other types of bacteremia in children; however, a relatively longer period was needed before an etiologic diagnosis could be made. This can be a result of the smaller volume of blood drawn from children for culture inoculation and the longer time needed for growth and identification of anaerobic organisms.

Certain other serious concomitant complications were also present in our patients. The most frequent complication was meningitis, which occurred in five patients. Peritonitis occurred in three patients, subdural empyema in two, and septic shock in one. Though many of the children were seriously ill, most responded well to therapy.

The mortality following anaerobic bacteremia in our series was 18% (five cases) and depended on such factors as age of the patient, underlying disease, nature of the organism, speed with which the diagnosis was made, and surgical or medical therapy instituted. This mortality was similar to that reported in adults.[9] Of the three infants who died, two were newborns

and one was 8 months old. Four patients were infected with organisms of the *B fragilis* group that were resistant to penicillin; inappropriate antimicrobial therapy was administered in two of these cases, due to the length of time needed for identification of the organisms; and the other two patients had underlying disorders that further aggravated their conditions. The fifth child who died had a ventriculoatrial shunt that was infected with *P acnes*, along with severe hydrocephalus and mental retardation.

Prolonged therapy with antimicrobial agents alone was apparently adequate for most patients. When anaerobes resistant to penicillin, such as the *B fragilis* group, are suspected or isolated, alternative medication such as clindamycin, chloramphenicol, carbenicillin, or ticarcillin disodium should be administered. Surgical drainage is essential when pus has collected. Organisms identical to those causing anaerobic bacteremia were recovered from other infected sites in 15 patients (58%). No doubt these extravascular sites may have served as a source of persistent bacteremia in some cases; however, the majority of patients recovered completely when prompt treatment with appropriate antimicrobial agents was instituted before any complications developed. The early recognition of anaerobic bacteremia and administration of appropriate antimicrobial and surgical therapy play a significant role in preventing mortality and morbidity in pediatric patients.

The staffs of the Clinical Microbiology Laboratories at Children's Hospital National Medica Center, Washington, DC, and the UCLA Medica Center provided help and cooperation; Linda Harteker, MS, assisted in the preparation of the manuscript.

Nonproprietary Names and Trademarks of Drugs

Ampicillin sodium—*Amcill-S, Omnipen-N, Penbritin-S for Injection, Polycillin-N for Injection, Principen/N.*
Ticarcillin disodium—*Ticar.*

References

1. Dunkle LM, Brotherton MS, Feigin RD: Anaerobic infections in children: A prospective study. *Pediatrics* 57:311-320, 1976.
2. Thirmuoothi MC, Keen BM, Dajani AS: Anaerobic infections in children: A prospective survey. *J Clin Microbiol* 3:318-323, 1976.
3. Brook I, Martin WJ, Cherry JD, et al: Recovery of anaerobic bacteria from pediatric patients: A one-year experience. *Am J Dis Child* 133:1020-1024, 1979.
4. Chow AW, Leake RD, Yamauchi T, et al: The significance of anaerobes in neonatal bacteremia: Analysis of 23 cases and review of the literature. *Pediatrics* 54:736-745, 1974.
5. Sanders DU, Stevenson J: *Bacteroides* infections in children. *J Pediatr* 72:673-677, 1968.
6. Martin WJ: Practical method for isolation of anaerobic bacteria in the clinical laboratory. *Appl Microbiol* 22:1168-1171, 1971.
7. Sutter VL, Vargo VL, Finegold SM: *Wadsworth Anaerobic Bacteriology Manual*, ed 2. Los Angeles, UCLA, 1975.
8. Holdeman LV, Moore WEC: *Anaerobic Laboratory Manual*, ed 3. Blacksburg, Va, Virginia Polytechnic Institute & State University, 1975.
9. Finegold, SM: *Anaerobic Bacteria in Human Disease.* New York, Academic Press Inc, 1977, chap 8 and 15.
10. Echeverria P, Smith AL: Anaerobic bacteremia observed in a children's hospital. *Clin Pediatr* 9:688-695, 1978.
11. Berry FA Jr, Yarbrough S, Yarbrough N, et al: Transient bacteremia during dental manipulation in children. *Pediatrics* 51:476-479, 1973.
12. DeLeo AA, Schoenknecht FD, Anderson MW, et al: The incidence of bacteremia following oral prophylaxis on pediatric patients. *Oral Surg* 37:36-45, 1974.
13. Beeler BA, Crowder JG, Smith JW, et al: *Propionibacterium acnes:* Pathogen in central nervous system infection. *Am J Med* 61:935-938, 1976.
14. Marchildon MB, Dudgeon DL: Perforating appendicitis: A current experience in Children's Hospital. *Ann Surg* 185:84-87, 1977.
15. Stone JH: Bacterial flora of appendicitis in children. *J Pediatr Surg* 11:37-42, 1976.
16. Alvack L, Wood HF, Fousek HD: Septicemia of the newborn. *Pediatr Clin North Am* 13:1131-1148, 1966.
17. Buetow KC, Klein SW, Lane RB: Septicemia in premature infants: The characteristics, treatment, and prevention of septicemia in premature infants. *Am J Dis Child* 110:29-41, 1965.
18. Alpern RJ, Dowell VR Jr: Nonhistotoxic clostridial bacteremia. *Am J Clin Pathol* 55:717-722, 1971.
19. Howard MF, Bradley JM, Flynn DM, et al: Outbreak of necrotizing enterocolitis caused by *Clostridium butyricum. Lancet* 2:1099-1102, 1977.
20. Pearson HE, Anderson GV: Perinatal deaths associated with *Bacteroides* infections. *Obstet Gynecol* 30:486-491, 1967.
21. Tynes BS, Frommeyer WB Jr: *Bacteroides* septicemia cultural, clinical, and therapeutic features in a series of 25 patients. *Ann Intern Med* 56:12-26, 1962.
22. Harrod JR, Sevens DA: Anaerobic infections in the newborn infant. *J Pediatr* 85:399-402 1974.
23. Robinow M, Simonelli FA: *Fusobacterium bacteremia* in the newborn. *Am J Dis Child* 110:92-94, 1965.
24. Brook I, Martin WJ, Finegold SM: Bacteriology of tracheal aspiration in newborns with perinatal pneumonia, meconium aspiration, and respiratory distress syndrome, abstracted. *Clin Res* 25:121a, 1977.
25. Donaldson SS, Moore MR, Rosenberg SA, et al: Characterization of postsplenectomy bacteremia among patients with and without lymphoma. *N Engl J Med* 287:69-71, 1972.
26. Goodman JS: *Bacteroides* sepsis, diagnosis and therapy. *Hosp Pract* 6:121-128, 1971.
27. Alpern RJ, Dowell VR Jr: *Clostridium septicum* infections and malignancy. *JAMA* 209:385-388, 1969.
28. Myerowitz RL, Medeiros AA, O'Brien TF: Bacterial infection in renal homotransplant recipients: A study of 53 bacteremic episodes. *Am J Med* 53:308-314, 1972.
29. Wilson WR, Martin WJ, Wilkowske CJ, et al: Anaerobic bacteremia. *Mayo Clin Proc* 47:639-646, 1972.
30. Felner JM, Dowell VR Jr: *'Bacteroides'* bacteremia. *Am J Med* 50:787-796, 1971.
31. Medeiros AA: *Bacteroides* bacillemia. *Arch Surg* 105:819-820, 1972.
32. Washington JA II: Relative frequency of anaerobes. *Ann Intern Med* 83:908, 1975.
33. Chow AW, Guze LB: Bacteroidacea bacteremia: Clinical experience with 112 patients. *Medicine* 53:93-126, 1974.

Cerebellar Ataxia, Opsoclonus, and Occult Neural Crest Tumor

Abdominal Computerized Tomography in Diagnosis

Morris Kinast, MD; Howard S. Levin, MD; A. David Rothner, MD; Gerald Erenberg, MD; Jeffrey Wacksman, MD; James Judge, DO

• A 9-month-old female with opsoclonus and ataxia was examined. Computerized axial tomography (CT) of her abdomen identified a retroperitoneal mass of neural crest origin that was not recognized by more conventional roentgenographic methods. The syndrome of cerebellar ataxia, myoclonus, and opsoclonus, and its relationship to neural crest tumors is reviewed along with the usefulness of abdominal CT.

(*Am J Dis Child* 134:1057-1059, 1980)

Opsoclonus, defined as periodic, jerking, ataxic, conjugate eye movements occurring in all planes, was first described in 1927 by Orzechowski.[1] The anatomic focus for opsoclonus is thought to be in the cerebellum.[2] Orzechowski noted the association of opsoclonus with cerebellar ataxia and myoclonus. Kinsbourne, in 1962, further described this triad in his report on six infants so affected.[3]

In 1968, Solomon and Chutorian[4] recognized the association of cerebellar ataxia, opsoclonus, and/or myoclonus with occult neuroblastoma. Today, it is generally accepted that a child with cerebellar ataxia and opsoclonus should be thoroughly examined for an occult neuroblastoma.

This article suggests that conventional radiology may not be sufficient for identification of all cases of occult neural crest tumors.

REPORT OF A CASE

A 9-month-old female was admitted for evaluation of opsoclonus and ataxia. She had been well until six weeks before admission when diarrhea developed and lasted five days. After the diarrhea cleared, the patient remained irritable and had intermittent jerky eye movements. One week later, truncal ataxia developed and became progressively worse. She was admitted to a local hospital where the examination included normal chest roentgenography, intravenous pyelography, electroencephalography, and computerized axial tomography (CT). The patient was treated with 40 IU of corticotropin, daily, with subsequent improvement of her eye movement and balance problems. She was then transferred to the Cleveland Clinic Foundation for further observation. The infant's prior development had been normal; she was able to attain a sitting position by herself and transfer objects from one hand to another.

On admission, physical examination showed an irritable child with frequent, intermittent jerking of her eyelids associated with chaotic eye movements. Extraocular movements were full. Muscle tone was markedly decreased. The patient had gross truncal ataxia and was barely able to sit alone when propped up. Mild limb ataxia was present. Deep tendon reflexes were normal. There was no myoclonus. The results of general examination were normal; no abdominal mass was palpable.

Laboratory findings included normal EEG, CT of the thorax, and 24-hour urine assay for catecholamines. The intravenous pyelogram (IVP) was also normal. Computerized tomography of the abdomen showed a mass of increased density in the mid-retroperitoneal space (Fig 1).

The patient underwent an exploratory laparotomy, and a 1.5 × 0.5 × 0.3-cm paraaortic retroperitoneal mass was excised. Postoperatively, she was treated with 30 mg of prednisone daily. After one month, the patient was beginning to pull herself to a sitting position; there were neither chaotic eye movements nor truncal ataxia, but there was persistent hypotonia. Three months after surgery, at which time she was receiving 5 mg of prednisone daily, the results of a neurologic examination were normal except for hypotonia. She was able to sit alone and pull herself to a standing position. The patient had a vocabulary of five words.

PATHOLOGIC FINDINGS

The resected specimen consisted of irregular, resilient, noncalcified, pink-white fibrous tissue with focal areas of brown nodularity. Microscopic examination showed nodules of mature neuroganglionic tissue, nerve, and fibroadipose tissue. The neurogan-

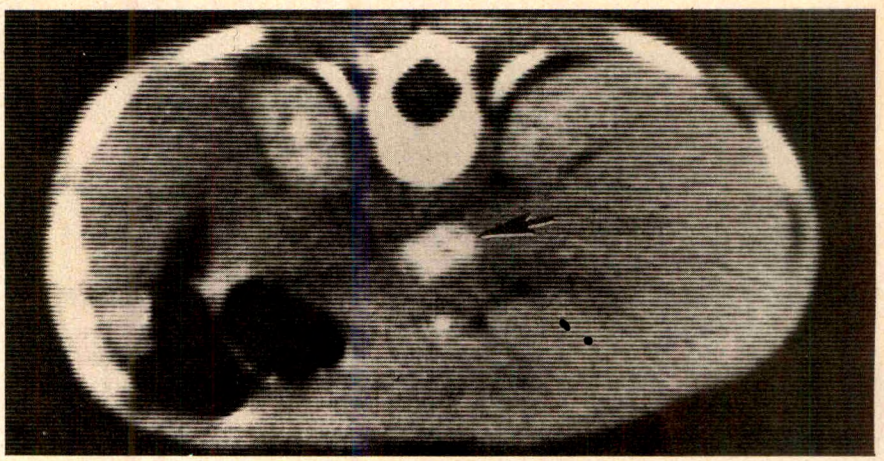


Fig 1.—Intravenous contrast-enhanced computerized tomogram of abdomen showing retroperitoneal mass (arrow).

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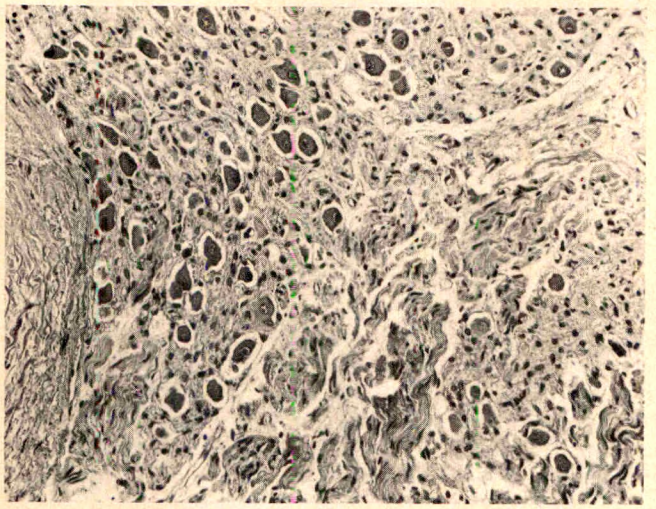

Fig 2.—Retroperitoneal mass showing benign ganglion cells admixed with Schwann cells growing, in part, in fascicular pattern (hematoxylin-eosin stain, original magnification ×200).

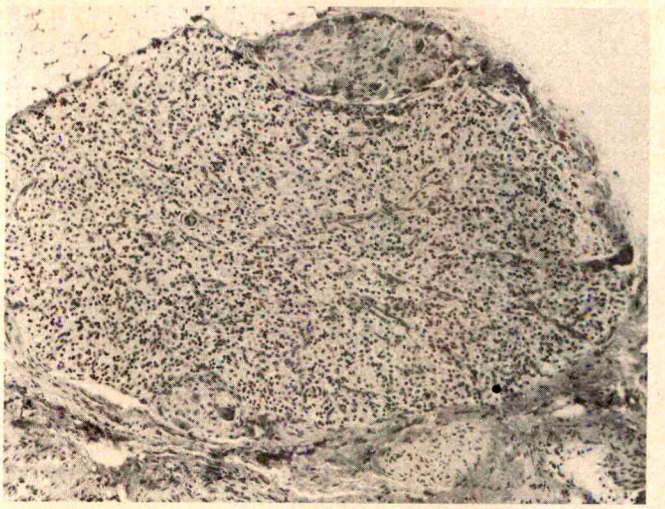

Fig 3.—Solitary, oval, 1.0-mm structure found at periphery of mass. It is encapsulated and divided by capillaries (hematoxylin-eosin stain, original magnification ×100).

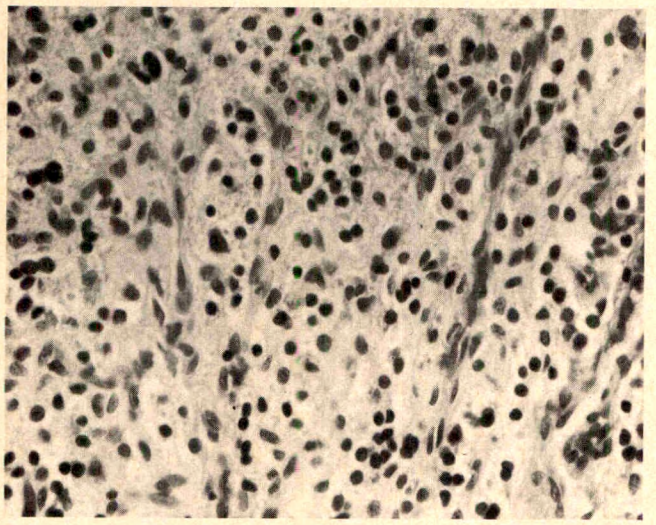

Fig 4.—Photomicrograph of Fig 3 at higher magnification. Elongated capillary structures divide nodule. These demarcate cells with round, dark nuclei and cells with more elongate vesicular nuclei. Cytoplasmic borders are indistinct and background has fibrillar character (hematoxylin-eosin stain, original magnification ×200).

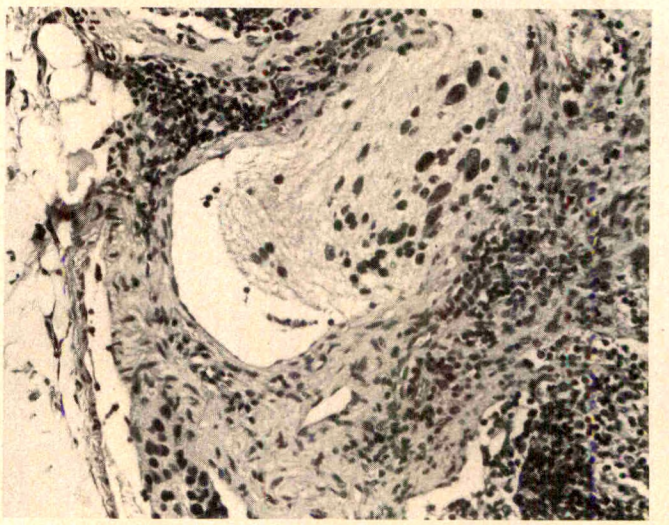

Fig 5.—Periphery of lymph node within retroperitoneal mass showing intrasinusoidal cells in eosinophilic, fibrillar background. Some cells are elongate, enlarged, and have character of ganglion cells (hematoxylin-eosin stain, original magnification ×200).

glionic tissue consisted of benign, mature ganglion cells and adjacent Schwann cells growing partly in a fascicular pattern (Fig 2). The ganglion cells contained reddish cytoplasm and vesicular nuclei with prominent nucleoli and fine chromatin. At the periphery of one section was a solitary, oval, 1.0-mm structure encapsulated by fine collagen and partly surrounded by neuroganglionic tissue (Fig 3). The structure was more cellular than the remainder of the tissue, lobulated, and divided by capillaries (Fig 4). Within roughly lobulated areas there were seen clusters of round cells with granular cytoplasm and dense nuclei that were the size of small lymphocytes. In the peripheral sinus of one lymph node, within a fibrillar eosinophilic background, there were cells of varied sizes with round to elongated nuclei and occasionally prominent nucleoli having the appearance of ganglion cells (Fig 5).

The original sections that did not show the ganglion-type cells in a lymph node were reviewed by several surgical pathologists, pediatric pathologists, and neuropathologists. Interpretations varied from ganglioneuroma with "neuroblastoma in situ" to benign neuroganglionic tissue with a paraganglial rest.

The discrete area believed by some to be neuroblastoma in situ appeared more organized, well defined, and noninvasive than the usual neuroblastoma. Although these cells had more abundant cytoplasm than the usual cells of neuroblastoma and although their appearance suggested a benign

paraganglial rest, the finding of immature ganglion cells in the peripheral sinus of a lymph node argued strongly for the neoplastic character of the lesion. The finding of fibrillar material and ganglion cells in the peripheral sinus of a lymph node suggested a maturing neural crest neoplasm. It was not possible to determine whether the tumor represented (1) a neuroblastoma that had metastasized and almost completely differentiated to a ganglioneuroma, (2) a ganglioneuroma with a neuroblastic focus from its inception, or (3) a tumor that was predominantly a mature ganglioneuroblastoma with local metastasis to a lymph node.

COMMENT

Acute cerebellar ataxia of childhood has many causes. When the ataxia is associated with opsoclonus there is often an occult neuroblastoma present. Roberts and Freeman[5] analyzed the methods of diagnosis of neuroblastoma in 25 reported cases of acute cerebellar ataxia and found that 56% were recognized by chest roentgenogram, 36% by physical examination, and 8% by abdominal roentgenogram. In our patient, no mass was recognized by any of these methods. In addition, results of an IVP and 24-hour urine assay for catecholamines were normal. The diagnosis was made only by CT of the abdomen. The usefulness of the body scanner for the diagnosis of abdominal lesions in children has been demonstrated by Leonidas et al.[6] In their study, however, abdominal CT and IVPs were abnormal in all patients with retroperitoneal masses. To our knowledge, our case is the first report of a retroperitoneal neural crest tumor diagnosed solely by abdominal CT.

Neuroblastomas are well known to undergo spontaneous regression by several mechanisms, including cytolysis and/or maturation into a ganglioneuroma.[7] Our patient's tumor was composed of predominantly mature neuroganglionic cells, with a single focus of cells thought to be neuroblastoma and a focus of ganglion cells in the peripheral sinus of a lymph node. It was not possible to determine whether the mass principally represented a ganglioneuroma from its inception or whether the tumor was a neuroblastoma that was differentiating into a ganglioneuroma. Had the tumor remained undiagnosed, it may have undergone spontaneous regression. Few autopsies have been performed on children with cerebellar ataxia and opsoclonus without associated neuroblastoma. It is tempting to speculate, as Bray et al[8] did, that some of these children actually have neuroblastomas that are undiagnosed by conventional techniques and subsequently undergo spontaneous regression. The unusual histologic findings in this case suggest the possibility that some of the reported cases of neuroblastoma and ganglioneuroblastoma in association with cerebellar ataxia represent entities that differ from the classic forms in histologic composition and biologic evolution. These cases should be assembled and critically reviewed in an attempt to identify the histologic and biologic features.

Surgical removal of the retroperitoneal mass resulted in dramatic improvement of our patient's neurologic problems. Such a favorable response, however, does not always occur, and it is possible that our patient will have a relapse. Neurologic deficits may persist despite complete surgical cure of the neuroblastoma. Senelick et al[9] reviewed 22 reported cases and found that only 18% of the patients became free of neurologic abnormalities after treatment of the neuroblastoma, 82% had residual cerebellar signs, and 36% were mentally retarded. Although the incidence of neurologic sequelae is high, the prognosis for survival is good. The two-year survival rate for children with neuroblastoma and cerebellar ataxia is reported to be 84% to 91% compared with a survival rate of only 10% to 29% for the overall number of patients with neuroblastoma. In both groups, the survival rate is best among children less than 1 year old at the time of diagnosis.[10]

The pathogenesis of the disorder is unknown. Postmortem examinations do not reveal tumor metastases to the cerebellum. In two reported necropsies of subjects with this syndrome, one showed mild demyelination adjacent to the dentate nucleus and another showed marked loss of Purkinje's cells.[11] Suggested pathogenetic mechanisms include (1) cross reaction of antibodies to the neural crest tumor with cerebellar cells, the resulting antigen-antibody reactions cause the cerebellar dysfunction; (2) infection of both neural crest tissue and the cerebellum with a neurotropic virus that causes both tumor formation and cerebellar dysfunction; and (3) release by the tumor of a metabolite that disrupts normal cerebellar function.[8]

We believe that if a child has cerebellar ataxia and opsoclonus, and conventional methods fail to identify a neoplasm, whole-body CT should be performed in an effort to determine if an occult neuroblastoma or other neural crest tumor exists.

Nonproprietary Name and Trademarks of Drug

Corticotropin—*Actest, Acthar, Actrope, Cortrophin, Duracton.*

References

1. Orzechowski C: De l'ataxic dysmétrique des yeux: Remarques sur l'ataxie des yeux dite myoclonique (opsoclonie, opsochorie) *J Fr Psychol Neurol* 35:1-18, 1927.
2. Ellenberger C Jr, Campa JF, Netsky MG: Opsoclonus and parenchymatous degeneration of the cerebellum: The cerebellar origin of an abnormal ocular movement. *Neurology* 18:1041-1046, 1968.
3. Kinsbourne M: Myoclonic encephalopathy of infants. *J Neurol Neurosurg Psychiatry* 25:271-276, 1962.
4. Solomon GE, Chutorian AM: Opsoclonus and occult neuroblastoma. *N Engl J Med* 279:475-477, 1968.
5. Roberts KB, Freeman JM: Cerebellar ataxia and 'occult neuroblastoma' without opsoclonus. *Pediatrics* 56:464-465, 1975.
6. Leonidas JC, Carter BL, Leape LL, et al: Computed tomography in diagnosis of abdominal masses in infancy and childhood: Comparison with excretory urography. *Arch Dis Child* 53:120-125, 1978.
7. Pochedly C: Neuroblastoma in infancy, in Pochedly C (ed): *Neuroblastoma.* Acton, Mass, Publishing Sciences Group, Inc, 1976, pp 1-35.
8. Bray PF, Ziter FA, Lahey ME, et al: The coincidence of neuroblastoma and acute cerebellar encephalopathy. *J Pediatr* 75:983-990, 1969.
9. Senelick RC, Bray PF, Lahey ME, et al: Neuroblastoma and myoclonic encephalopathy: Two cases and a review of the literature. *J Pediatr Surg* 8:623-632, 1973.
10. Altman AJ, Baehner RL: Favorable prognosis for survival in children with coincident opso-myoclonus and neuroblastoma. *Cancer* 37:846-852, 1976.
11. Moe PG, Nellhuas G: Infantile polymyoclonia-opsoclonus and neural crest tumors. *Neurology* 20:756-764, 1970.

Local Immunity in Mumps Meningitis

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• Titers of antibodies to mumps and measles virus and interferon activity were measured in sera and CSF obtained from 15 children with mumps meningitis. Antibody to mumps virus was found in 11 of 15 CSF samples. Evaluation of the CSF-serum ratio for antibodies to both viruses showed a substantially higher ratio for antibody to mumps virus. The ratio of IgG/IgM antibody activity to mumps virus was greater in CSF than in sera. These results could be attributed to antibody synthesis, particularly IgG, in the CNS. Titers of antibodies to mumps virus in CSF increased rapidly, reaching a peak four to ten days from onset of meningitis, and swiftly decreased thereafter. During the acute phase, interferon activity was found in almost all cases ranging from 16 to 128 IU/mL in sera, and 4 to 16 IU/mL in CSF. In cases of mumps meningitis that followed the usual clinical course, interferon disappeared within a week, whereas it persisted in the CSF in cases of persistent pleocytosis.

(*Am J Dis Child* 134:1060-1064, 1980)

It is well known that many viruses can invade the CNS and cause various diseases (eg, meningitis, encephalitis, postinfection encephalitis, and degenerative diseases).[1] In some cases, the mortality is high and the sequelae serious. While the recent development of effective vaccines has resulted in prevention of many viral diseases,[2] once an infection of the CNS is established, effective treatment is virtually impossible. It is still unclear how the host defense mechanisms work to eliminate the virus at the infected site.

Using experimental animals, research on the local humoral and cellular immunity of the CNS has been undertaken,[3-5] and it has become clear that cerebral tissues are capable of independent immunologic responses to viral infection. However, aside from some cases such as subacute sclerosing panencephalitis[6] and meningitis caused by echovirus,[7] studies in humans are scarce.

We have obtained paired sera and CSF from children with mumps meningitis. Using these samples, we studied the production of antibody in the CNS and changes in interferon activity in CSF during infection.

SUBJECTS AND METHODS

Patients

The study group consisted of 15 children with mumps meningitis and three with mumps parotitis in which meningitis did not occur. The children were between 3 and 11 years old. They were admitted to the pediatric wards of Nagoya University Hospital, Handa Hospital, Anjo Hospital, and Okazaki Hospital from May 1977 to June 1978. Fifteen of the 18 were male. The diagnosis of mumps parotitis was based on the typical swelling of the parotid gland and serologic evaluation. The diagnosis of meningitis in these children was confirmed by clinical manifestation (fever, headache, vomiting, and stiff neck) and by lymphocytic pleocytosis in their CSF several days after the onset of parotitis. The cell count of CSF ranged from 115 to 1,160 cells/cu mm and the percentage of mononuclear cells ranged from 50% to 100%. Four of the children, cases 12 through 15 in Table 1, showed persistent pleocytosis (cell count, ≥100/cu mm seven to ten days after the onset of meningitis). Although clinical symptoms persisted for a few days in these four cases, all patients recovered completely within three weeks after the onset.

Materials

Sera and CSF that were collected within a few hours of each other were obtained from patients in both the acute and convalescent phases. All specimens were stored at −20 °C until tested.

Hemagglutination Inhibition (HI) Test

Paired serum and CSF specimens were examined, in parallel, for hemagglutinating antibodies to mumps and measles virus. The HI test was based on that described by Rosen.[8] The titers are given as the reciprocal of the maximum dilutions of serum or CSF that showed HI activity. Serum dilutions started at 1:10 for mumps virus and 1:16 for measles virus. Dilutions of CSF were started at 1:2. Blood-stained or xanthochromic samples of CSF were not tested.

Indirect Immunofluorescence

To determine the class specificity of the antibodies to mumps virus, an

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Table 1.—Hemagglutination Inhibition (HI) Titer of Antibodies to Mumps and Measles Virus in Convalescent Sera and CSF of 15 Patients With Mumps Meningitis

Case No.	Mumps, HI Titer			Measles, HI Titer			Days After the Onset of Meningitis*
	Serum		CSF	Serum		CSF	
1	20	:	2	< 16	:	< 2	11
2	80	:	< 4	128	:	< 2	10
3	80	:	2	128	:	< 2	9
4	320	:	8	32	:	< 2	8
5	320	:	16	< 16	:	< 2	14
6	80	:	< 2	128	:	< 2	10
7	40	:	2	< 16	:	< 2	14
8	80	:	2	≥ 256	:	< 2	8
9	80	:	< 2†	256	:	2	15
10	20	:	< 2	128	:	< 2	15
11	40	:	< 4†	32	:	< 2	11
12	320	:	< 2	64	:	< 2	13
13	160	:	4	32	:	< 2	25
14	320	:	16	64	:	< 2	12
15	80	:	2	256	:	2	10

*Indicates time between onset of meningitis and the day the samples were collected.
†During the acute phase of meningitis (four or five days after onset) HI antibodies to mumps virus were found with titers of 2.

indirect immunofluorescent assay was performed as described previously.[9] Mumps virus-infected monkey kidney cells were used as antigens. Serial dilutions of CSF and sera from five patients, and fluorescein isothiocyanate-conjugated antihuman IgG and IgM were used as the primary and secondary antibodies, respectively.

Interferon Assay

To assay interferon, CSF and sera were dialyzed overnight at a pH of 2; the pH was adjusted to a pH of 7.0 before assay. The assay was performed according to the cytopathic effect inhibition method in FL cell[10] monolayers, using vesicular stomatitis virus (VSV) as a challenge virus. A modification of the semi-micromethod described by Havell and Vilček was used.[11] Individual wells of a 96-well tissue culture plate were first filled with 50 μL of Eagle's minimum essential medium (MEM). From each sample 50 μL was added to the first well that contained an equal volume of medium, and twofold serial dilutions were made using an automatic diluter. Each well was then seeded with 50,000 FL cells in 50 μL of MEM supplemented with 5% fetal calf serum (FCS). After 20 hours of incubation at 37 °C in a 5% CO_2 incubator, the media was discarded and each well was then infected with 100 units of a 50% tissue culture infective dose ($TCID_{50}$) of VSV in 100 μL of MEM and FCS. The cells were observed microscopically 36 to 48 hours after inoculation of the virus. At this time, the control cells showed complete destruction by the virus. The highest dilutions of the sample that caused 50% protection of cells were considered the end points. In this microassay, 1 interferon unit/mL was equal to 2.0 IU/mL. Each sample of CSF of serum was titrated in duplicate. To check species specificity of this activity, mouse L cells[12] were used as target cells.

RESULTS

HI Antibody Titer in Sera and CSF

Table 1 gives HI titers of antibodies to mumps virus in convalescent sera and CSF from 15 children with mumps meningitis. All of the sera were positive for antibodies to mumps virus with titers ranging from 20 to 320. Of the 15 CSF samples, nine were positive with titers ranging from 2 to 16. Cases 9 and 11 did not have antibodies to mumps virus in convalescent CSF; however, antibodies were present during the acute phase of meningitis with titers of 2. To summarize, antibody to mumps virus was found in 11 of 15 samples of CSF during the illness.

Table 1 also gives the HI titer of antibodies to measles virus. Except for three cases (case 1, 5, and 7), titers of 32 or more were found in sera, whereas, in CSF, an HI titer of two could be detected in only two cases. The CSF-serum ratios of antibodies to mumps and measles virus were determined. The antibody ratios for mumps virus ranged from approximately 1:20 to 1:40. The antibody ratios for measles virus were clearly lower, as shown by a substantial difference in the CSF-serum ratio for the two viruses.

Antibodies to mumps virus were found in sera from three patients with uncomplicated mumps meningitis at titers ranging from 40 to 160, but there was no evidence of antibody activity in their CSF.

IgG and IgM Fluorescent Antibody (FA) Titer

To determine the class of immunoglobulin in CSF and sera, indirect immunofluorescence was performed. Table 2 gives FA titers of IgG and IgM to mumps virus in five patients' CSF and sera. In four cases, the ratio of IgG/IgM FA titer was greater in CSF than in sera. This result suggests that the antibody response in the CNS may be dominated by IgG synthesis.

Kinetics of Antibodies to Mumps Virus

The change in HI titer of antibodies to mumps virus with time was investigated in sera and CSF. Figure 1 shows the HI titer to mumps virus in sera and CSF of the 15 cases in terms of days after the onset of meningitis. As shown in this figure, in all sera, the

Table 2.—Fluorescent Antibody (FA) Titer in Sera and CSF of Five Patients With Mumps Meningitis

Case No.	Days From Onset of Meningitis*	FA Titer	
		Serum, IgG/IgM	CSF, IgG/IgM
4	8	256/128	4/< 2
5	14	64/32	16/< 4
13	13	64/64	8/2
14	7	128/64	8/4
15	10	32/128	2/< 2

*Indicates time between onset of meningitis and the day the samples were collected.

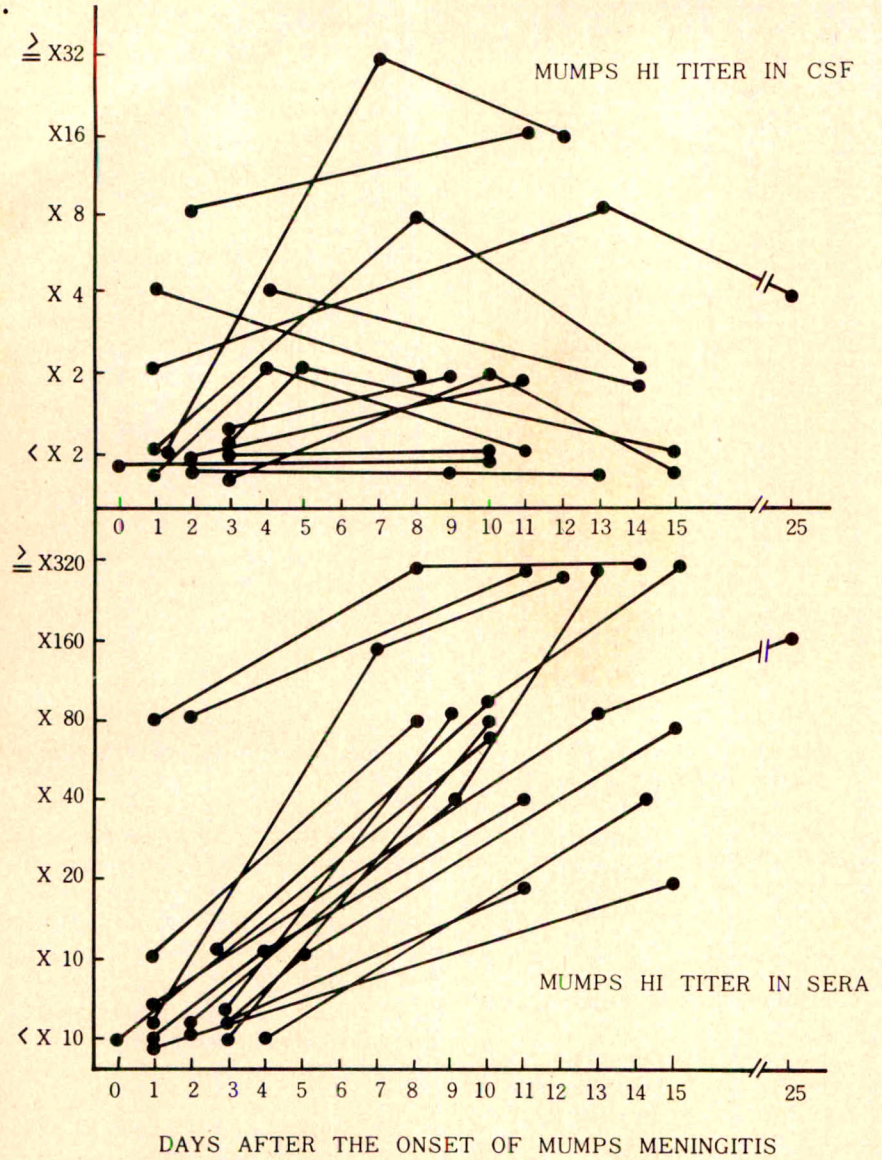

Fig 1.—Kinetics of antibodies to mumps virus in sera and CSF from 15 patients with mumps meningitis. HI indicates hemagglutination inhibition.

antibody titer increased during the convalescent phase over that seen in the acute phase. Antibodies in the CSF, however, were detected very early (one to two days after onset) in three cases. By day 4 to 10 the antibody titer peaked in many cases and sharply declined thereafter. Only one case possessed antibodies in the CSF 25 days after the onset of the illness. Thus, the antibody titer in CSF rose at first but soon declined; an obvious difference from the serum antibody response. These studies indicate that an independent humoral immune response occurs in the cerebral cavity in mumps meningitis.

Interferon Activity

Figure 2 shows interferon levels in sera and CSF of the 15 patients with mumps meningitis. In the acute phase, 16 to 128 interferon units/mL were found in all serum samples. In many cases, these levels disappeared within ten days. On the other hand, in 14 of 15 CSF samples, 4 to 16 interferon units/mL were detected in the acute phase. In cases that followed the usual clinical courses of mumps meningitis, such levels declined by about day 7. However, in four patients with persistent pleocytosis, three (cases 12, 14, and 15, indicated by asterisk) continued to display interferon activity for seven to ten days. During this time, no interferon activity could be found in their sera. Interferon levels in the CSF diminished gradually, corresponding to the improvement of the CSF pleocytosis. In the three cases of uncomplicated mumps meningitis, however, no CSF interferon was detected during the infection.

The Role of Mononuclear Cells in CSF

To study the role of mononuclear cells in CSF, the relationship between the mononuclear cell count and HI titer of antibodies to mumps virus in CSF was examined. No positive correlation was apparent ($r = -.36$); however, there was a definite positive correlation between the mononuclear cell count and the interferon titer in CSF ($r = +.73$). Thus, it is believed that the greater the mononuclear cell populations, the higher the titer of interferon in CSF.

COMMENT

Viral infections of the CNS, while not frequent, can become very serious. As yet, there is no effective treatment available, with the possible exception of the use of vidarabine in cases of encephalitis due to herpes simplex virus.[13] In order to find an effective treatment, it is necessary to ascertain what defense mechanism operates at the actual site of virus invasion, which factor is activated first among immune systems, and what factor is blocked in a serious illness.

Recent experiments using mice have provided data on the role of local immunity in viral infections of the CNS. Hapel and Gardner[4] reported that in mouse meningitis caused by ectromelia virus, cytotoxic T cells appear in the CSF. We have found that in the cases of vaccinia meningitis in mice, 80% of the mononuclear cells appearing in the meninges are T cells, 12% are macrophages, while B cells are extremely rare.[14] These local T cells were observed to be virus-specific and were cytotoxic to vaccinia virus-infected cells. It has been suggested that the cell-mediated immunity in the brain can be separated from other systemic immune activities.

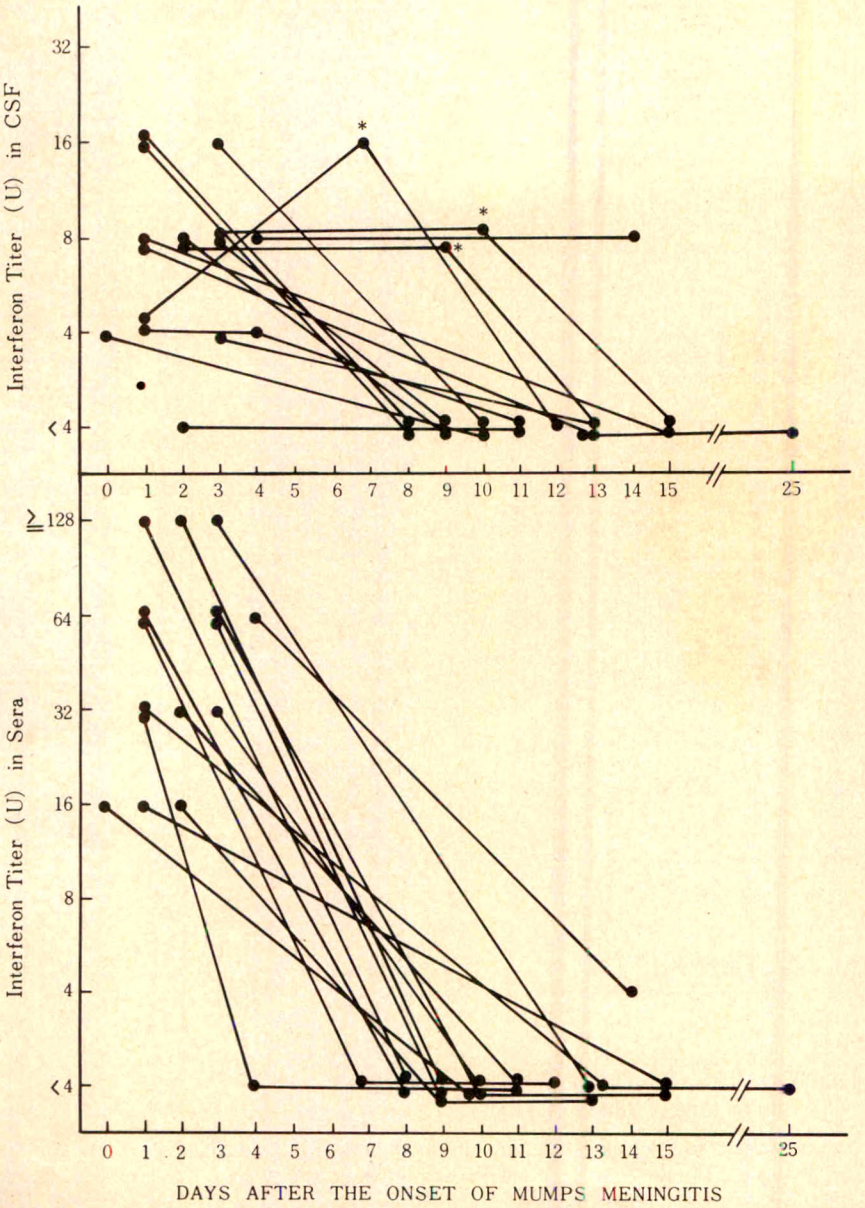

Fig 2.—Kinetics of interferon activity in sera and CSF from 15 patients with mumps meningitis. Asterisk indicates cases with persistent pleocytosis and prolonged interferon production in CSF. In our assay system, 1 interferon unit/mL was equal to 2.0 IU/mL.

Gerhard et al,[15] in their investigations of humoral immunity in viral infections of the CNS, studied immunoglobulin subtypes in CSF from mice infected with parainfluenza virus type 1 and concluded that independent antiviral antibody production occurred in the CNS. In cases of subacute sclerosing panencephalitis in humans, the observation of high titers of antibodies to measles virus in CSF was found to be due to independent production of antibody within the CNS.[6] However, reports on the immune responses of CNS in the case of ordinary acute viral infections are relatively rare.[7,16]

In this article, we have discussed antibody and interferon production in the CNS in cases of mumps meningitis. Comparison of the titers of antibodies in CSF and serum during the convalescent phase showed that the CSF-serum ratio of antibodies to mumps virus was higher than the ratio for measles virus. Therefore, antibodies to mumps virus in CSF are not caused by some serum antibody influx, but by the independent production of antibody within the CNS. Investigations of the transition in antibody production in CSF showed that antibody activity in CSF increased rapidly, reached a peak at four to ten days from the onset, and swiftly declined thereafter. Thus, the kinetics of antibody production in CSF were quite different from those in serum. In addition, the IgG/IgM ratio was greater in CSF than in sera. Therefore, IgG synthesis may be predominant in the CNS. This result coincides with the recent article by Frydén and Link.[17]

Gresser and Naficy[18] reported the existence of interferon activity in CSF in viral diseases of the CNS. However, to date, the role of local interferon has been unclear. We also found that interferon was present in CSF at a concentration of 4 to 16 IU/mL in the acute phase of mumps meningitis and disappeared within ten days. Long-lasting interferon production was detected in three cases of persistent pleocytosis. However, this prolonged interferon production disappeared with the improvement of the pleocytosis. In these cases, it is possible that interferon production continued because of the viral antigens that may have remained so long in the meninges. From these results, we propose that interferon activity in the brain might be a key factor in curbing the local spread of a virus. A positive relationship exists between these interferon levels and the mononuclear cell count in CSF, so these cells might contribute to interferon production in the CNS (in our unpublished data, these mononuclear cells are mainly T cells).

Recent studies on the mechanism of interferon production divide interferon into at least two types. Type 1, or standard interferon, is produced by nonlymphoid and lymphoid cells in response to viruses, polynucleotides, and endotoxin.[19] Type 2, or immune interferon, is a mediator of cellular immunity, a lymphokine, and produced by sensitized lymphocytes in response to specific antigens or antigen-antibody complexes.[20-22] The interferon measured in our laboratory was type 1 interferon, since the activ-

ity was found after treatment at a pH of 2. However, it is possible that type 2 interferon was also produced during these infections and was destroyed by the treatment at a pH of 2. Hooks et al[23] suggest that the production of type 2 interferon may contribute to immunologic aberrations in autoimmune diseases and may also protect the already compromised host from further viral infections. The role of type 2 interferon in viral infections of the CNS, particularly in those infections that are chronic or subchronic, should be investigated further.

John J. Hooks, PhD, Laboratory of Oral Medicine, National Institute of Dental Research, and Janice D. Longstreth, PhD, Laboratory of Microbial Immunity, National Institute of Allergy and Infectious Disease, National Institutes of Health, gave advice and assistance in preparation of this manuscript.

References

1. Fenner FJ, White DO: *Medical Virology*, ed 2. New York, Academic Press Inc, 1976, pp 461-466.

2. Barkin RM: Measles mortality: A retrospective look at the vaccine era. *Am J Epidemiol* 102:341-349, 1975.

3. Lipton HL, Gonzalez-Scrano F: Central nervous system immunity infected with Theiler's virus: I. Local neutralizing antibody response. *J Infect Dis* 137:147-151, 1978.

4. Hapel A, Gardner I: Appearance of cytotoxic T cells in cerebrospinal fluid of mice with ectromelia virus-induced meningitis. *Scand J Immunol* 3:311-319, 1974.

5. Ogra PL, Ogra SS, Al-Nakeeb S, et al: Local antibody response to experimental poliovirus infection in the central nervous system of rhesus monkeys. *Infect Immun* 8:931-937, 1973.

6. Metha P, Kane A, Thormar H: Quantitation of measles virus-specific immunoglobulins in serum, CSF and brain extract from patients with subacute sclerosing panencephalitis. *J Immunol* 118:2254-2261, 1977.

7. Ogra PL: Distribution of echovirus antibody in serum, nasopharynx, rectum, and spinal fluid after natural infection with echovirus type 6. *Infect Immun* 2:150-155, 1970.

8. Rosen L: Hemagglutination and hemagglutination-inhibition with measles virus. *Virology* 13:139-141, 1961.

9. Morishima T, Ichikawa T, Yamaguchi H, et al: Acute infantile gastroenteritis caused by rotavirus in Japan. *Eur J Pediatr* 129:259-265, 1978.

10. Fogh J, Lund R: Continuous cultivation of epithelial cell strain (FL) from human amniotic membrane. *Proc Soc Exp Biol Med* 94:532-537, 1957.

11. Havell EA, Vilček J: Production of high-titered interferon in cultures of human diploid cells. *Antimicrob Agents Chemother* 2:476-484, 1972.

12. Earle WR, Schilling EL, Stark TH, et al: Production of malignancy in vitro: IV. The mouse fibroblast cultures and changes seen in the living cells. *J Natl Cancer Inst* 4:165-212, 1943.

13. Whitley RJ, Soong SJ, Dolin R, et al: Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. *N Engl J Med* 297:289-294, 1977.

14. Morishima T, Hayashi K: Meningeal exudate cells in vaccinia meningitis of mice: Role of local T cells. *Infect Immun* 20:752-759, 1978.

15. Gerhard W, Iwasaki Y, Koprowski H: Central nervous system-associated immune response to parainfluenza type 2 virus in mice. *J Immunol* 120:1256-1260, 1978.

16. Frydén A, Link H, Moller E: Demonstration of cerebrospinal fluid lymphocytes sensitized against virus antigens in mumps meningitis. *Acta Neurol Scand* 57:396-404, 1978.

17. Frydén A, Link H: Predominance of oligoclonal IgG type lambda in CSF in aseptic meningitis. *Arch Neurol* 36:478-480, 1979.

18. Gresser I, Naficy K: Recovery of an interferon-like substance from cerebrospinal fluid. *Proc Soc Exp Biol Med* 117:285-289, 1964.

19. Baron S, Dianzani F: General considerations of the interferon system. *Tex Rep Biol Med* 35:1-10, 1977.

20. Youngner JS, Salvin SB: Production and properties of migration inhibitory factors and interferon in the circulation of mice with delayed hypersensitivity. *J Immunol* 111:1914-1922, 1973.

21. Valle MJ, Jordan GW, Haahr S, et al: Characteristics of immune interferon produced by human lymphocyte cultures compared to other human interferons. *J Immunol* 115:230-233, 1975.

22. Fujibayashi T, Hooks JJ, Notkins AL: Production of interferon by immune lymphocytes exposed to herpes simplex virus-antibody complexes. *J Immunol* 115:1191-1193, 1975.

23. Hooks JJ, Moutsopoulos HM, Geis SA, et al: Immune interferon in the circulation of patients with autoimmune disease. *N Engl J Med* 301:5-8, 1979.

60 YEARS AGO IN THE AJDC

A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children

A group of seventeen patients is reported who appeared with a combination of painful and red hands and feet, photophobia and redness of the eyes, restlessness, and at times delirium combined with alopecia, anorexia, and emaciation proceding to death. All were young children under 4 years of age and five were under a year. No fever or acute symptoms were described. There was no tendency to clustering geographically and the cases were seen in each of the preceding five years. Several patients died but the total number of deaths is not given. The clinical picture was one of misery: children would lie abed rubbing hands and feet, apathetic, and wretched. The tender hands, however, appeared to have diminished sensitivity to pinprick. The rash commonly went on to exfoliation. The finger and toe nails were entirely unaffected. Hair loss was caused by children pulling out hair by the handful. Teeth were commonly lost spontaneously with no prior apparent disease, caries, or gum disease. Mild leukocytosis occurred in some cases. There were several children who had a urinary tract infection. The disorder lasted from two to eight months. Treatment was of little avail. A number of children were gavage fed, thought to be of some benefit. No effect was derived from diphtheria antitoxin. Removal of diseased tonsils and adenoids appeared effective in some cases.

Various etiologies were discussed. Pellagra, while similar in some respects, was dismissed as less likely. Arsenic poisoning was excluded by study of the urine. Influenza, prevalent at the time, was considered but did not seem to have occurred in others living with the children and few had significant respiratory symptoms. Acrodynia or "epidemic erythema" was thought to have a number of features in common with this disorder.—Albert H. Byfield, MD, Department of Pediatrics, College of Medicine, State University of Iowa, Iowa City (20:347-365, November 1920).

Progressive Facial Hemiatrophy

Report of a Case Associated With Ewing's Sarcoma

Jan E. Paradise, MD; R. Beverly Raney, Jr, MD; Linton A. Whitaker, MD

• A child with progressive facial hemiatrophy (PFHA) later had Ewing's sarcoma develop. During seizures presumably related to her PFHA, she suffered pathologic fractures on two occasions. The second of these might have been avoided had her condition been better understood.

(*Am J Dis Child* 134:1065-1067, 1980)

Progressive facial hemiatrophy (PFHA) was first described by Parry[1] and Romberg[2] in the mid-19th century. Although PFHA generally begins during childhood, no mention of it appears in standard pediatric textbooks, and we have found only two references to it in the pediatric literature, on succeeding pages of a single publication.[3,4] Prompt recognition of PFHA is important, not only because effective cosmetic management is available, but also because failure to appreciate its various complications—in particular, unusual manifestations of epilepsy—may result in delayed or inappropriate therapy. We report an illustrative case—additionally noteworthy because the patient had a malignant tumor that to our knowledge has not previously been reported in association with PFHA—and review the salient features of the disease.

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REPORT OF A CASE

A 13-year-old girl had experienced, at 4 years of age, right facial hemiatrophy that became progressively more severe. At 5 years, she had received a graft of a portion of rib to the right maxillary area, and at 6 years, she received a silicone elastomer implant to the right cheek. The implant was subsequently removed because of chronic local infection. By 7 years of age, the atrophy had become static. Figure 1 shows her appearance at age 12.

At 12 years of age, the patient began to complain of gradually increasing pain in the left thigh. Roentgenograms showed a mottled, lytic lesion of the left ischium, and biopsy specimens from the lesion revealed Ewing's sarcoma. Chest and skeletal roentgenograms and a bone scan showed no evidence of metastatic disease. Treatment was started with vincristine sulfate and cyclophosphamide in accordance with regimen 3 of the Intergroup Ewing's Sarcoma Study.[5] One month later, she experienced a generalized seizure, followed immediately by severe pain in the left hip. The seizure was considered a complication of vincristine therapy, and roentgenograms of the hip showed a pathologic fracture of the left acetabulum with protrusion of the femur into the pelvic aperture. Open surgical reduction was carried out. During the next four months, she was kept in a spica cast and received both radiotherapy to the pelvis (5,500 rads) and prophylactic pulmonary radiation (1,500 rads).

Two months later, the patient was hospitalized again because of severe back pain that developed immediately after an auditory hallucination and a second major motor seizure. Careful questioning disclosed that since her first seizure she had been experiencing frequent isolated auditory hallucinations in the form of spoken voices of family members and telephone-ringing sounds. On examination, she appeared cachectic and was comfortable only in the supine position. Marked alopecia was present. The right side of her face below the orbit, and the adjacent subcutaneous tissues of the neck, were atrophied and distorted. The involved facial skin had areas of both hypopigmentation and hyperpigmentation. The left side of the face and neck appeared normal. Flexion of the left hip was limited, and there was marked tenderness to palpation over the lumbar spine. The deep tendon reflexes were diminished, but no other neurologic abnormalities were found.

Facial roentgenograms showed, on the right, absence of the zygoma and hypoplasia of the maxilla and mandible. The mandible was rotated superiorly and laterally, and the condylar process was atretic (Fig 2). Roentgenograms showed generalized osteoporosis, pulmonary hilar adenopathy suggestive of metastatic disease, and a compression fracture of the body of the fourth lumbar vertebra. Since a bone scan at that time was normal, the fracture was attributed to osteoporosis. An EEG and brain scan were normal. A presumptive diagnosis of temporal lobe epilepsy as a

Fig 1.—Appearance of patient at age 12 years.

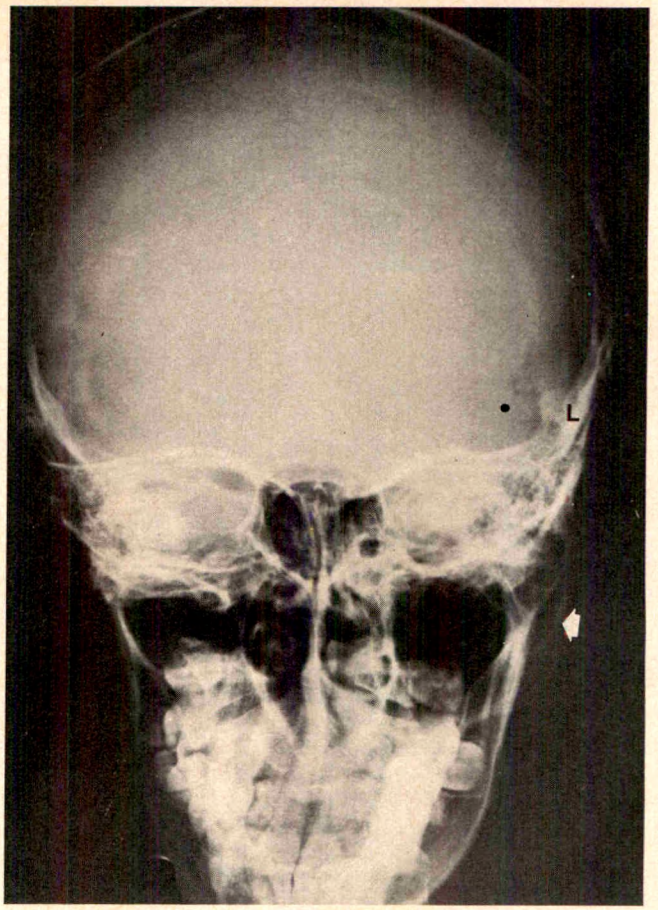

Fig 2.—Skull film of patient showing absence of zygoma and hypoplasia of maxilla and mandible on right (arrow indicates left zygoma). Mandible is rotated superiorly and laterally and condylar process is atretic.

complication of PFHA was made, and the patient was discharged on a regimen of rest, phenobarbital, and meperidine hydrochloride.

Five weeks later, roentgenograms showed that the patient had bilateral femoral metastases as well as enlargement of the previously suspected pulmonary metastases. Her family and physicians agreed that further chemotherapy should not be undertaken. The patient died at home nine months after her tumor had been diagnosed. Permission for an autopsy was not given.

COMMENT

In the present case, the history of progressively developing facial hemiatrophy is similar to that in cases reported in the surgical literature.[6,7] In addition, the present case illustrates a complication, temporal lobe epilepsy, the accurate diagnosis of which may depend on the physician's awareness of its association with this disease. Since a description of PFHA cannot be found in standard textbooks of pediatrics, neurology, or pathology, or in the general pediatric literature, a review of its features for pediatricians and others caring for children appears in order.

The disease consists of idiopathic, acquired, unilateral atrophy of the face, variably involving skin, fat, connective tissue, muscle, and bone. Occasionally, the atrophy extends to the opposite side of the face or to the ipsilateral extremities, and a variety of clinical patterns have been described.[6-8] A distinctive histologic diagnosis of PFHA is not possible in the absence of the clinical pattern, since scleroderma similarly may be characterized by atrophy of both dermis and epidermis, flattening or absence of rete pegs, inflammatory changes, and excessive collagen formation.[9,10]

Generally, PFHA begins during the first or second decade; and among reported cases, female patients predominate slightly.[6] The disease has been described in blacks,[4] whites,[8] and orientals.[11] No genetic predisposition is apparent, although there have been a few reports of familial occurrence.[6,12] The right and left sides of the face are involved equally often.[6,7]

Many hypotheses have been advanced concerning the cause of PFHA. Local trauma and infection have been incriminated as precipitating events, but neither convincingly.[7] Wartenberg considered PFHA an heredodegenerative disease,[8] while Moss and Crikelair[13] produced PFHA in rats by performing unilateral cervical sympathectomies. For the present, the cause of PFHA in humans must be considered unknown.

Clinically, the atrophic process in PFHA usually begins with a focal pigmentary change or a gradual

"sinking-in" of subcutaneous tissue in the paramedian area of the face. The disease progresses over periods ranging from several weeks to a decade or longer before eventually becoming static. Characteristic is a sharp, vertical delineation between the two sides of the face, termed "coup de sabre" (saber stroke). The degree of deformity varies widely. More severe outcomes have been thought to develop in patients whose atrophy starts before facial bone growth has been completed.[6,7]

The complications of PFHA are principally ocular and neurologic. Ocular complications occur in more than 10% of patients, and include enophthalmos, extraocular muscle weakness, iridocyclitis, and refractive changes.[3,7,12,14] Neurologic complications include Horner's syndrome, trigeminal neuralgia, migraine, and epilepsy, especially Jacksonian motor and sensory types.[8-15] Epilepsy characteristically occurs late in the course and is associated with variable EEG findings.[11] To our knowledge, the development of a malignant tumor in a child with PFHA has not been described heretofore; for this reason, no inherent relationship can be inferred in the present case between the Ewing's sarcoma and the PFHA.

The differential diagnosis of PFHA includes congenital abnormalities, posttraumatic and postsurgical atrophy, subcutaneous fat necrosis, partial lipodystrophy, and musculocutaneous atrophy secondary to cranial nerve paralysis.[9] Crikelair et al[16] have attempted to discriminate among types of facial hemiatrophy on the basis of cephalometric measurements.[16] For the clinician, perhaps the most difficult diagnostic task is to differentiate PFHA from morphea, or localized scleroderma. The clinical course may clarify the diagnosis, since PFHA eventually becomes static. However, some authors believe that scleroderma and PFHA may be variations of a single disease process.[7,8]

The deformity produced by PFHA is often severe and psychologically trying. Dimethylpolysiloxane fluid (liquid silicone) injected subcutaneously may be used to correct small defects, but its use has been associated with high rates of infection and extrusion.[17] More recently, techniques using bone and soft-tissue grafts have allowed more successful reconstructive efforts.

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Nonproprietary Name and Trademark of Drug

Vincristine sulfate—*Oncovin*.

References

1. Parry CH: *Collections From the Unpublished Medical Writings*. London, Underwoods, 1825, vol 1, p 478.
2. Romberg MH: *Klinische Ergebnisse*. Berlin, A Forstner, 1846, pp 75-81.
3. Hussels IE, Knox DL: Hemifacial atrophy. *Birth Defects* 7:292, 1971.
4. Harper PS: Hemifacial atrophy (the Romberg syndrome). *Birth Defects* 7:293, 1971.
5. Perez CA, Razek A, Tefft M, et al: Analysis of local tumor control in Ewing's sarcoma: Preliminary results of a cooperative intergroup study. *Cancer* 40:2864-2873, 1977.
6. Rogers BO: Progressive facial hemiatrophy: Romberg's disease, a review of 772 cases. *Excerpta Medica Int Cong Ser* 66:681-689, 1964.
7. Rees TD: Facial atrophy. *Clin Plast Surg* 3:637-646, 1976.
8. Wartenberg R: Progressive facial hemiatrophy. *Arch Neurol Psychiatry* 54:75-96, 1945.
9. Rees TD: Facial hemiatrophy in childhood, in Mustardé JC (ed): *Plastic Surgery in Infancy and Childhood*. Philadelphia, WB Saunders Co, 1971, pp 326-330.
10. Robbins SL: *Pathologic Basis of Disease*. Philadelphia, WB Saunders Co, 1974, p 243.
11. Miyazaki M, Shimazaki K: The electroencephalogram of facial hemiatrophy. *Clin Neurol* 14:723-727, 1974.
12. Franceschetti A, Koenig H: L' importance du facteur hérédo-dégénératif dans l hémiatrophie faciale progressive (Romberg): Étude des complications oculaires dans ce syndrome. *J Genet Hum* 1:27-64, 1952.
13. Moss ML, Crikelair GF: Progressive facial hemiatrophy following cervical sympathectomy in the rat. *Arch Oral Biol* 1:254-258, 1959.
14. Karny H, Baum JL: Refractive change as the initial sign of progressive facial hemiatrophy. *Am J Ophthalmol* 79:878-879, 1975.
15. Gorlin RJ, Pindborg JJ, Cohen MM: *Syndromes of the Head and Neck*, ed 2. New York, McGraw-Hill Book Co, 1976, pp 341-344.
16. Crikelair GF, Moss ML, Khuri A: Facial hemiatrophy. *Plast Reconstr Surg* 29:5-13, 1962.
17. Rees TD, Ashley FL, Delgado JP: Silicone fluid injections for facial atrophy: A ten-year study. *Plast Reconstr Surg* 52:118-127, 1973.

Plasma Adrenocorticotrophic Hormone in Congenital Adrenal Hyperplasia

Importance in Long-term Management

Stephen LaFranchi, MD

• **In a prospective study, assays of plasma adrenocorticotrophic hormone (ACTH) were compared with established criteria to evaluate the determination's usefulness in monitoring the control of congenital adrenal hyperplasia (CAH). In 22 infants and children with 21-hydroxylase deficiency, the plasma ACTH value correctly identified the status of control in 51 of 73 (70%) patient visits. Plasma ACTH concentrations were significantly higher in patients whose conditions were out of control when compared with patients whose conditions were under control, although there was an overlap between the two groups. Plasma ACTH concentrations were significantly higher in patients with sodium-losing CAH than in patients with non-sodium-losing CAH. These findings support the concepts that patients with the sodium-losing condition have a more severe enzyme deficiency and that ACTH stimualtion may be affected by sodium balance. Although plasma ACTH determinations are a useful adjunct in the long-term management of CAH, they cannot be relied on as the sole criterion of control.**

(*Am J Dis Child* 134:1068-1072, 1980)

In the most common type of congenital adrenal hyperplasia (CAH), a deficiency of the enzyme 21-hydroxylase results in decreased cortisol production, that reduces negative feedback on the pituitary gland, leading to increased production of adrenocorticotrophic hormone (ACTH). Previous reports have documented increased plasma ACTH concentrations in both untreated and treated patients with CAH.[1-6]

In the treatment of CAH, the appropriate dose of glucocorticoids is based on evaluation of traditional criteria, including growth velocity, presence or absence of virilizing signs or cushingoid changes, rate of skeletal maturation, and 24-hour urinary 17-ketosteroid (17-KS) and pregnanetriol (PT) excretion.[7] Serum 17-α-hydroxyprogesterone (17-OHP), although it is the best diagnostic test, cannot be relied on alone to determine adequacy of control.[8] More recently, the usefulness of plasma renin activity has been reported.[5] Despite careful management with established criteria, a proportion of infants and adolescents still have growth problems, inappropriate or early virilization, irregular menses, and infertility.[9-13] Also, 24-hour urine collections in infants and children are difficult to obtain and can be inaccurate.

Since suppression of plasma ACTH into the normal range may represent the most sensitive end point of optimal glucocorticoid therapy, a study was undertaken to assess the usefulness of plasma ACTH determinations in monitoring long-term control of 22 infants and children with CAH.

METHODS

The study population of 22 patients represented all infants and children with CAH followed up at the University of Oregon Health Sciences Center, Portland. All 22 had 21-hydroxylase deficiency; 16 had sodium-losing CAH (12 boys and four girls) and six had non-sodium-losing CAH (two boys, and four girls). The patients ranged in age from 2 weeks to 16½ years and were followed up for a mean of 18 months (range, three to 27 months) during the study. Three of the patients, two infants with sodium-losing CAH and one 6½-year-old girl with non-sodium-losing CAH were studied before and after treatment.

Plasma ACTH was determined by the radioimmunoassay method of Rees et al.[14] The ACTH assay was regularly sensitive to concentrations of 20 pg/mL, with intra-assay and interassay coefficients of variation of 2.2% and 15.2%, respectively. In a group of control subjects, the mean plasma ACTH value was 54 pg/mL at 8 AM and 29 pg/mL at 4 PM. Urinary 17-KS were assayed by the method of Drekter et al[15] and PT was assayed by the method of Cox.[16] Serum 17-OHP values were determined by radioimmunoassay.[17] Bone age was determined according to the standards of Gruelich and Pyle.[18] Statistical comparisons were performed using the Student's *t* test.

The patients were evaluated at three- to six-month intervals. Plasma samples for ACTH were routinely obtained between 9 and 11 AM. The 24-hour urine specimens were usually collected the previous day, although occasionally a period of one to two weeks existed between urine collection and plasma sampling. Adequacy of glucocorticoid dosage was assessed by the following criteria: (1) growth velocity, (2) bone age advancement, (3) 24-hour urinary 17-KS, and (4) 24-hour urinary PT. The assessment of whether conditions were being controlled or out of control was based on all of the above criteria. In controlled conditions, growth velocity or bone age advancement was within 2 SDs of the mean for age, whereas in uncontrolled conditions, these values were greater than 2 SDs above mean; 24-hour urinary 17-KS and PT were under control if the values were within the normal range for age, whereas they were out of control if abnormally elevated for age. When all four criteria or three of the four criteria were in agreement, the patient's condition was assessed as being in control or out of control, as indicated. When two of the criteria disagreed with

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the other two so that an assessment of control was not definite, the plasma ACTH value obtained at this visit was not used for data analysis.

Treatment comprised cortisone acetate or hydrocortisone, approximately 25 mg/sq m/day, with one third of the dose administered in the morning and two thirds at bedtime. In addition, the patients with sodium-losing CAH received fludrocortisone acetate, 0.05 to 0.15 mg/day. Individual adjustments in glucocorticoid dosage were made based on results of the above studies.

• RESULTS

The results of plasma ACTH assays in the 22 infants and children with CAH are presented in Fig 1. Plasma ACTH concentrations ranged from 10 to 2,218 pg/mL (normal, 10 to 100 pg/mL) in these children receiving treatment. When patients' conditions were judged to be controlled by previously established criteria, the plasma ACTH value was normal in 27 of 34 samplings. When patients' conditions were judged to be out of control, the plasma ACTH value was abnormally elevated in 24 of 39 measurements. Plasma ACTH concentrations (mean ± SEM) were significantly higher in out-of-control conditions (334 ± 82 pg/mL) than in controlled conditions (87 ± 15 pg/mL) ($P < .01$). Patients with sodium-losing CAH whose conditions were out of control had significantly higher plasma ACTH concentrations (372 ± 95 pg/mL) than those whose conditions were in control (83 ± 15 pg/mL) ($P < .01$). However, the plasma ACTH concentration was not significantly different in patients with non-sodium-losing CAH whose conditions were out of control (124 ± 50 pg/mL) than in those whose conditions were in control (122 ± 66 pg/mL). Also, the plasma ACTH value was significantly higher ($P < .02$) in all samples from patients with sodium-losing CAH (234 ± 53 pg/mL) when compared with all samples from patients with non-sodium-losing CAH (123 ± 38 pg/mL). When the plasma ACTH value was plotted against the corresponding 24-hour urinary 17-KS or PT concentrations, no significant correlations were obtained.

The results of plasma ACTH, 24-hour urinary 17-KS and PT, and serum 17-OHP in three patients at the time of diagnosis, before treatment and after treatment, are shown in the Table. In two infants with newly diagnosed sodium-losing CAH, the elevated plasma ACTH value was suppressed into the normal range in nine days and two months, respectively. In the 6½-year-old girl with non-sodium-losing CAH, two plasma ACTH determinations prior to treatment did not show any diurnal variation, and they

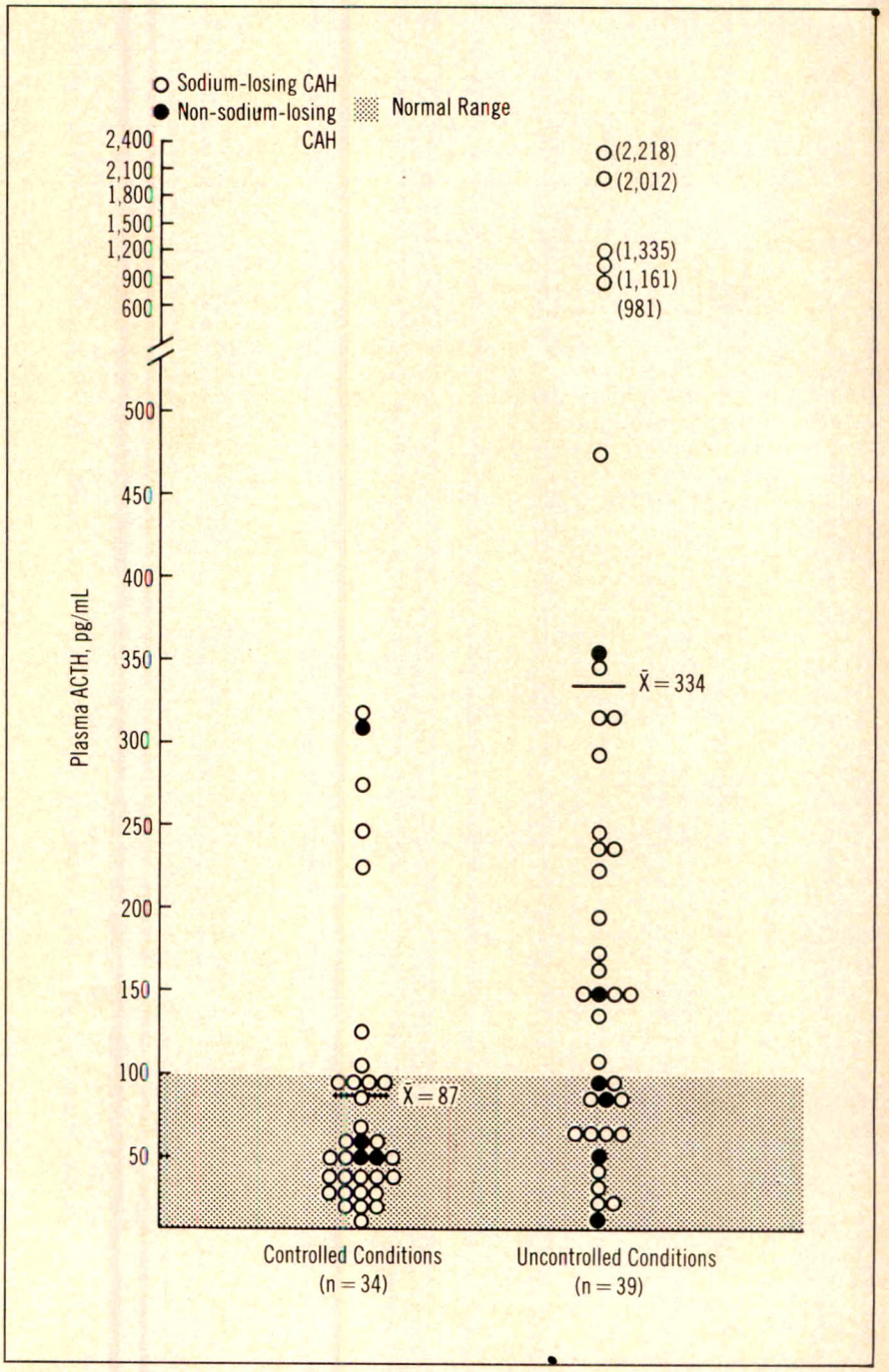


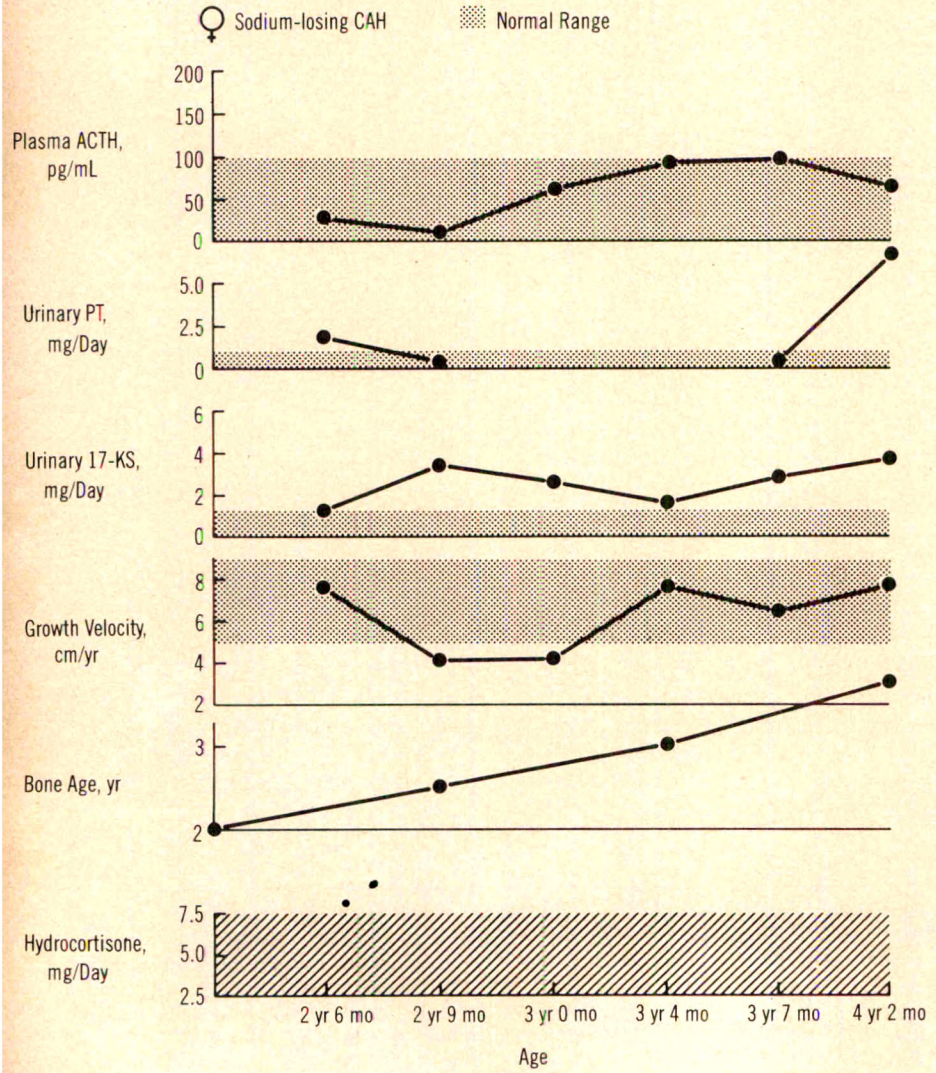
Fig 1.—Plasma adrenocorticotrophic hormone (ACTH) concentrations in controlled and uncontrolled conditions. In controlled conditions, growth velocity and bone age advancement were within 2 SDs of mean for age and 24-hour urinary 17-ketosteroid (17-KS) and pregnanetriol (PT) values were normal for age. Conditions were out of control if growth velocity and bone age advancement were beyond 2 SDs of mean and urinary 17-KS and PT were abnormally elevated for age. CAH indicates congenital adrenal hyperplasia.

Laboratory Values in Sodium-Losing and Non-Sodium-Losing Congenital Adrenal Hyperplasia (CAH)*

Patient/Condition	Age	Urinary Excretion 17-KS, mg/Day	Urinary Excretion PT, mg/Day	Serum 17-OHP, ng/mL	Time	Plasma ACTH, pg/mL	Treatment†
1/sodium-losing CAH	19 days	28.0	4.2	752	9 AM	348	None
	28 days	0.1	. . .	. . .	10 AM	40	Hydrocortisone, 24 mg
2/sodium-losing CAH	20 days	7.5	0.1	539	9:45 AM	1,161	None
	3 mo	0.4	0.1	. . .	10 AM	< 37	Hydrocortisone, 12 mg
3/non-sodium-losing CAH	6 yr 7 mo	8.1	4.0	. . .	7 AM	74	None
					5 PM	85	None
	6 yr 7 mo‡	3.2	0.6	. . .	7 AM	65	Dexamethasone, 2 mg
Normal range	. . .	0-2	0-1	0-3	. . .	10-100	. . .

*17-KS indicates 17-ketosteroids; PT, pregnanetriol; 17-OHP, 17-α-hydroxyprogesterone.
†Total 24-hour dose of medication.
‡Obtained three days after pretreatment studies.

Fig 2.—Results of determinations of plasma adrenocorticotrophic hormone (ACTH), 24-hour urinary 17-ketosteroid (17-KS) and pregnanetriol (PT), growth velocity, and bone age in girl with treated sodium-losing congential adrenal hyperplasia (CAH) from chronological age 2 years 3 months to 4 years 2 months. Shaded area for growth velocity includes mean ± 2 SDs.



were in the normal range. At 7 AM, the serum cortisol value was 10 μg/dL at the time when the plasma ACTH value was 74 pg/mL. The plasma ACTH value showed little change after three days of dexamethasone treatment, 2 mg daily (65 pg/mL).

Some of the difficulty in determining the status of control and the usefulness of plasma ACTH concentrations is illustrated by the patient data in Fig 2 and 3. In Fig 2, plasma ACTH values, 24-hour urinary PT and 17-KS excretion, growth velocity, bone age, and hydrocortisone dosage are shown for a girl with sodium-losing CAH from the ages of 2½ to 4 years 2 months. Between 2½ years and 3 years 7 months, growth velocity, bone age maturation, and 24-hour urinary PT excretion were usually normal, the 24-hour urinary 17-KS values were mildly elevated, and the plasma ACTH concentrations ranged from 21 to 100 pg/mL. At 4 years 2 months, the growth velocity was 7.6 cm/yr and the bone age had advanced from 3 years to 3 years 8 months (at chronological ages 3 years 4 months to 4 years 2 months), yet the 24-hour urinary 17-KS concentration was 3.8 mg and the PT concentration was 5.8 mg (both of these values are elevated). Thus, two criteria indicated good control while two criteria indicated poor control, and the importance of the plasma ACTH concentration of 63 pg/mL could not be determined.

In Fig 3, similar studies are presented for a boy with sodium-losing CAH from the ages of 4 years 5

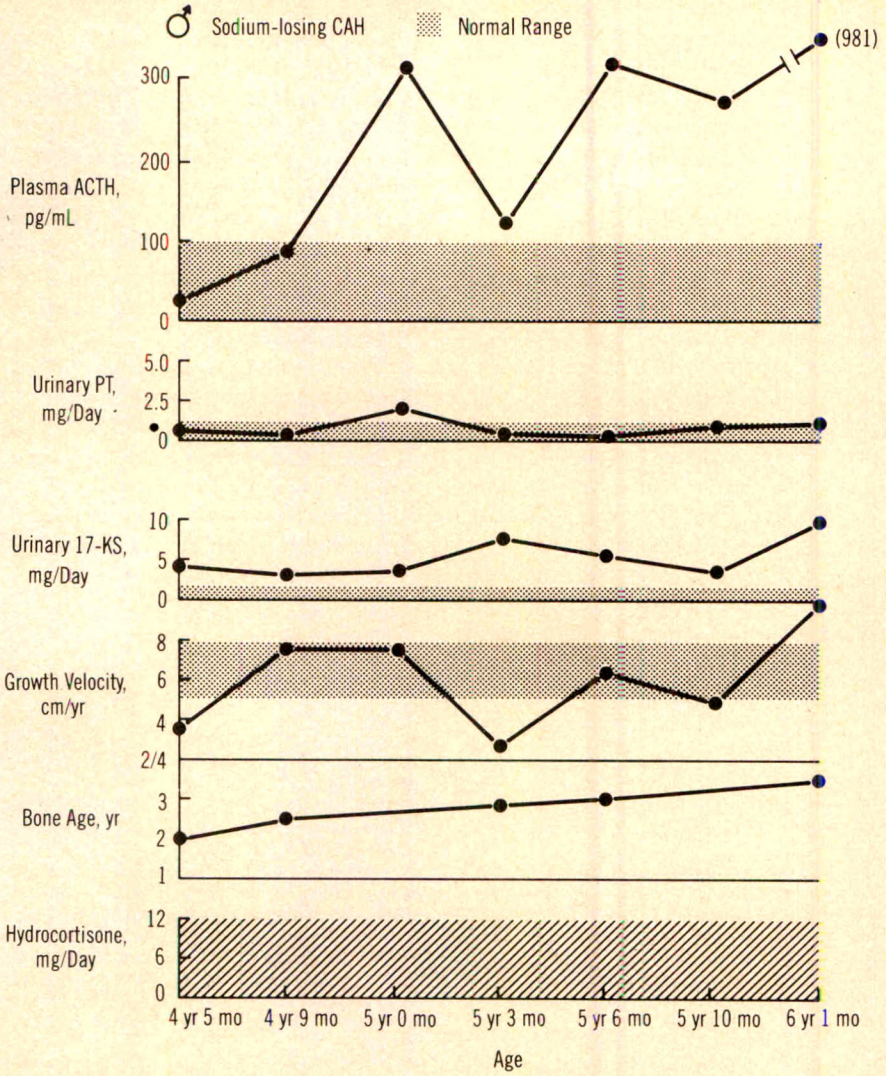


Fig 3.—Results of determinations of plasma adrenocorticotrophic hormone (ACTH), 24-hour urinary 17-ketosteroid (17-KS) and pregnanetriol (PT), growth velocity, and bone age in boy with treated sodium-losing congenital adrenal hyperplasia (CAH) from chronological age 4 years 5 months to 6 years 1 month. Shaded area for growth velocity includes mean ± 2 SDs.

months to 6 years 1 month. The patient's condition was judged to be in control at 4 years 5 months (plasma ACTH value, 27 pg/mL) and at 4 years 9 months (plasma ACTH value, 87 pg/mL), whereas at 5 years his condition was judged to be out of control (plasma ACTH value, 319 pg/mL). At 5 years 3 months, the growth velocity fell to 2.4 cm/yr, the bone age was 2 years 8 months, representing an increase of 4 months during the last half year, and the 24-hour urinary PT concentration was 0.4 ng, yet the 24-hour urinary 17-KS value was 7.6 mg. Since three of four values were normal or suppressed, the patient's condition was judged to be in control; the plasma ACTH value was mildly elevated at 126 pg/mL. At 5½ years and at 5 years 10 months, the patient's condition was judged to be in control on the basis of three of four criteria, yet the plasma ACTH value was even more elevated at 317 pg/mL and 273 pg/mL, respectively. Finally, at 6 years 1 month, the patient's condition was judged to be out of control: the growth rate was 10 cm/yr, he had elevated urinary 17-KS and PT values, and the plasma ACTH level was elevated to 981 pg/mL.

COMMENT

When plasma ACTH measurements were obtained along with other traditional criteria to evaluate control in infants and children with CAH, it correctly identified the status of control in 70% (51/73) of patient visits. Although plasma ACTH concentrations were significantly higher in patients whose conditions were judged to be out of control than in patients with controlled conditions, there was an overlap in values between these groups. As a whole, plasma ACTH concentrations were also significantly higher in samples from patients with sodium-losing CAH than from patients with non-sodium-losing CAH, and the highest ACTH levels were seen in patients with sodium-losing CAH. This finding is similar to that of Rösler et al[5] and lends support to their notion that the degree of ACTH stimulation is proportional to the degree of enzymatic deficiency; patients with sodium-losing CAH appear to have a greater deficiency of 21-hydroxylase.

As evidenced by Fig 1 through 3, the plasma ACTH value may be normal when other criteria indicate that the condition is out of control, or it may be elevated when the condition seems to be controlled. Although the explanation of these aberrant situations is not known, there are several possibilities. Some patients whose conditions were in good control may have neglected to take their morning dose of glucocorticoid. The lack of medication for 12 to 14 hours may have resulted in an elevated plasma ACTH value. In patients with treated CAH, Pham-Hun-Trung et al[6] found plasma ACTH concentrations of up to 475 pg/mL 12 to 14 hours after the last dose of glucocorticoid. Plasma ACTH values should be determined two to four hours after the morning dose of glucocorticoid. It is also possible that episodic secretion of plasma ACTH produced some variability in the results. Fukushima et al[19] reported that plasma ACTH values, when sampled every 20 minutes, varied through a tenfold range (12 to 120 pg/mL) between 12 noon and 4 PM in patients with untreated 21-hydroxylase deficiency. A more important explanation when conditions seem to be in good control but the plasma ACTH concentration is elevated may be subclinical

sodium wasting. Rösler et al[5] reported that a low sodium diet produced excessively high levels of plasma renin activity in children with CAH. They found that the degree of ACTH stimulation significantly correlated with the levels of plasma renin activity and was proportional to the degree of sodium loss. Although none of our patients had clinical manifestations of sodium loss or hypovolemia, this may explain seemingly paradoxically elevated plasma ACTH concentrations. These situations would indicate a need to determine plasma renin activity and adjust mineralocorticoid therapy if necessary.

As seen in case 1 in the Table, the pituitary-adrenal axis would appear to respond rapidly to glucocorticoid administration. The plasma ACTH value was normal nine days after treatment was started, and perhaps this normalization would have been seen sooner had it been evaluated. It is unclear why the initial plasma ACTH value in patient 3 (Table), a non-sodium-loser, was not elevated. As previously stated, plasma ACTH concentrations are lower in patients with non-sodium-losing CAH. Fukushima et al[19] have reported normal plasma ACTH concentrations in untreated patients with non-sodium-losing CAH. The patients with non-sodium-losing CAH probably have a milder, partial enzymatic deficiency. Once the adrenal glands hypertrophy, these patients are able to secrete adequate amounts of cortisol under basal conditions, as was the case in patient 3. It may be that the initially high ACTH secretion is inhibited as more cortisol is produced by the hypertrophied adrenal as pituitary-adrenal homeostasis occurs. Although a normal amount of ACTH would be sufficient to stimulate secretion of physiologic amounts of cortisol in these situations of mild enzymatic deficiencies, this would not be the case with the sodium-losing condition, which represents a more severe enzyme deficiency.

From this study it can be concluded that plasma ACTH is a useful adjunct in long-term management of CAH. However, it cannot be relied on as the sole criterion of control, and established studies should continue to be the main criteria of control.

Monte Greer, MD, performed the plasma ACTH measurements.

References

1. Demura H, West CD, Nugent CA, et al: A sensitive radioimmunoassay for plasma ACTH levels. *J Clin Endocrinol Metab* 26:1297-1302, 1966.
2. Berson SA, Yalow RS: Radioimmunoassay of ACTH in plasma. *J Clin Invest* 47:2725-2751, 1968.
3. Orth DN, Island DP, Nicholson WE, et al: ACTH radioimmunosasay: Interpretation, comparison with bioassay, and clinical application, in Hayes RL, Goswitz FA, Murphey BEP (eds): *Radioisotopes in Medicine: In Vitro Studies*. Oak Ridge, Tenn, US Atomic Energy Commission, Division of Technical Information, 1968, pp 251-272.
4. Cacciari E, Cicognani A, Pirazzoli P, et al: GH, ACTH, TSH, LH, and FSH reserve in prepubertal girls with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 43:1146-1152, 1976.
5. Rösler A, Levine LS, Schneider B, et al: The interrelationship of sodium balance, plasma renin activity, and ACTH in congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 45:500-512, 1977.
6. Pham-Hun-Trung MT, Gourmelen M, Raux-Eurin MC, et al: Pituitary-adrenal axis activity in treated congenital adrenal hyperplasia: Static and dynamic studies. *J Clin Endocrinol Metab* 47:422-426, 1978.
7. Bongiovanni AF, Root AN: The adrenogenital syndrome. *N Engl J Med* 208:1283-1289, 1963.
8. Lippe BM, LaFranchi SH, Lavin N, et al: Serum 17-α-hydroxyprogesterone, progesterone, estradiol, and testosterone in the diagnosis and management of congenital adrenal hyperplasia. *J Pediatr* 85:782-787, 1974.
9. Migeon CJ: Updating the treatment of congenital adrenal hyperplasia. *J Pediatr* 73:805-806, 1968.
10. Sperling MA, Kenny FM, Schutt-Aine TC, et al: Linear growth and hormonal responsiveness in treated congenital adrenal hyperplasia. *Am J Dis Child* 122:408-413, 1971.
11. Raiti S, Newns GH: Linear growth in treated congenital adrenal hyperplasia. *Arch Dis Child* 46:376-378, 1971.
12. Klingensmith GJ, Garcia SC, Jones HW Jr, et al: Glucocorticoid treatment of girls with congenital adrenal hyperplasia: Effects on height, sexual maturation, and fertility. *J Pediatr* 90:996-1004, 1977.
13. Urban MD, Lee PA, Migeon CJ: Adult height and fertility in men with congenital virilizing adrenal hyperplasia. *N Engl J Med* 299:1392-1396, 1978.
14. Rees LH, Cook DM, Kendall JW, et al: A radioimmunoassay for rat plasma ACTH. *Endocrinology* 89:254-261, 1971.
15. Drekter JJ, Heisler A, Scism GR, et al: The determination of urinary steroids: I. The preparation of pigment-free extracts and a simplified procedure for the estimation of total 17-ketosteroids. *J Clin Endocrinol Metab* 12:55-65, 1952.
16. Cox RI: A method for the quantitative determination in urinary extracts of C_2, 17:20-dihydroxy-20-methyl-steroids. *Biochem J* 52:339-345, 1952.
17. Abraham GE, Manlimos FS, Solis M, et al: Combined radioimmunoassay of four steroids in 1 ml of plasma: I. Progestins. *Clin Biochem* 8:369-373, 1975.
18. Gruelich WW, Pyle SI: *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford, Calif, Stanford University Press, 1959.
19. Fukushima DK, Finkelstein JW, Yoshida K, et al: Pituitary-adrenal activity in untreated congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 40:1-12, 1975.

Review Article

Diets for Children and Adolescents That Meet the Dietary Goals

Johanna Dwyer, DSc

• **The parents of many elementary and secondary schoolchildren ask pediatricians for advice on how to feed diets that are in line with the US *Dietary Goals* or the *Dietary Guidelines for Americans.* This article outlines an approach for planning diets that fit these recommendations while also assuring that intakes approximate the recommended dietary allowances and the estimated safe and adequate intakes of nutrients provided by the Food and Nutrition Board, National Research Council.**

(*Am J Dis Child* 134:1073-1080, 1980)

In the past decade, American parents became increasingly concerned about weight control, appropriate levels of fat, cholesterol, sugar, protein, vitamins, and minerals in family diets, and other issues related to health promotion and disease prevention.[1-3] Following the publication of recommendations directed to the lay public by various government bodies during the past three years, interest in these topics increased. All of these publications include advice about avoiding imbalance or excesses with respect to intakes of nutrients,[4-7] whereas previous dietary guidance only dealt with the issues of getting enough of the essential nutrients and avoiding obesity.[8-11] The Dietary Goals for the United States, issued by the Senate Select Committee on Nutrition and Human Needs in 1977, recommends specific dietary levels for the type and amount of fat, protein, and carbohydrate and amount of cholesterol and sodium to be consumed, as well as an exhortation to achieve energy balance.[4] Publications of the executive agencies of government, including the Surgeon General's report,[5,12] the USDA's new food guide,[6] and the joint USDA-Health, Education, and Welfare *Dietary Guidelines for Americans*,[7] provide more general guidance about these same constituents in the diet and sometimes include other information on health promotion. But few of them provide specific assistance in planning such diets for children.[12-14] Parents, like Jason and his Argonauts, are left without precise navigational advice to chart a course between the Scylla of insufficiency and the Charibdis of dietary excess for their offspring. As a result, they frequently turn to their pediatricians for dietary guidance.

The *Dietary Goals*, and to a lesser extent the subsequent publications that addressed these issues, gave rise to vigorous debate in professional circles.[15-28] Today, some pediatricians are urging their patients to follow some or all of the "goals," while others remain skeptical. Benefits deriving from following the guidelines are difficult to estimate since the efficacy of the measures vary, and are further influenced in a favorable manner by the adoption of other preventively oriented behaviors.[24] Similarly, the calculus of risks is not entirely clear for children and adolescents, although for adults, they pose little risk and some promise of benefit.[18] If the *Dietary Goals* were taken as the only source of dietary guidance, shortfalls in intakes of some protective micronutrients such as vitamins and minerals might arise that would pose risks to child health.[25] In any event, there is little doubt that diets for children and adolescents need to be chosen with care. When the *Dietary Goals* or similar guides are used, even more attention to planning is warranted, since additional constraints are placed on the choice of foods.

Until now, few dietary patterns have been published that are specifi-

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cally designed for children and assure sufficiency of micronutrient intakes while also achieving the desiderata for type and amount of fat, carbohydrate, and amounts of cholesterol, sodium, and energy that are outlined in the *Dietary Goals*.

A first approximation toward such patterns is presented herein. For pediatricians who have decided that such regimens are suitable for children of primary school age or older, this article offers practical advice about how to proceed in helping parents plan such diets in line with other relevant information about appropriate dietary intakes of children. For pediatricians who are unconvinced about the merits of such patterns, information on present intakes of children and adolescents is summarized, and suggestions about child diet and life-style practices are provided.

PRESENT DIETS OF CHILDREN AND ADOLESCENTS

Data on the usual dietary intakes and nutritional status of children and adolescents collected during the Ten-State Nutrition Survey[29] and the Health and Nutrition Examination Survey (HANES)[30] revealed that shortfalls in intakes of certain nutrients, as well as related indices of health status, did exist. In the ten-state survey, which focused on those in low income groups, primary schoolchildren in the poverty groups surveyed were judged to have a medium to high prevalence of deficient values for iron, and retarded growth and development. In addition, black and Spanish-American children had a medium to high prevalence of low serum riboflavin values, and Spanish-American children also exhibited similar indices for vitamin A nutriture. The HANES survey, which included all income groups, found that while mean micronutrient intakes were generally satisfactory, 30% or more of the primary schoolchildren had intakes below the levels specified in the recommended dietary allowances for iron, vitamin A, and ascorbic acid as being appropriate. Among adolescents, those interviewed in the ten-state survey showed a medium to high prevalence of nutrition problems related to iron. Subgroups showed similar shortfalls of riboflavin (blacks, Spanish Americans), and indices indicative of obesity (white male children). Adolescent's micronutrient intakes in the HANES survey generally approximated the recommended allowances, but 30% or more of the adolescents had iron, vitamin A, and ascorbic acid intakes below the standard; and girls aged 12 to 17 also exhibited similar shortfalls for protein and calcium. A substantial proportion of all children had particularly low energy intakes, although overt malnutrition was rare and obesity quite common, suggesting that energy outputs were lower, and/or energy

Table 1.—Intakes of Children Aged 6 to 11 Years in Health and Nutrition Examination Survey

	Food Group*				
	Milk	Meat	Breads and Cereals	Fruits and Vegetables	Fats, Sweets, or Alcohol
% of total calories	23	15	26	11	23
Provides 20% or more of total intakes of:					
Total fat	X	X			X
Saturated fat	X	X			
Cholesterol	X	X			
Sodium			X		
Sugar					X
Protein	X	X	X		
Calcium	X				
Phosphorus	X		X		
Iron		X	X		
Vitamin A	X			X	
Thiamin			X		
Niacin		X	X		
Riboflavin	X		X		
Ascorbic acid				X	

*Food group mentioned provides 20% or more of the constituent in question.

Table 2.—Intakes of Adolescents Aged 12 to 17 Years in Health and Nutrition Examination Survey

	Food Group*				
	Milk	Meat	Breads and Cereals	Fruits and Vegetables	Fats, Sweets, or Alcohol
% of total calories	21	16	25	11	25
Provides 20% or more of total intakes of:					
Total fat	X	X			X
Saturated fat	X	X			
Cholesterol	X	X			
Sodium			X		
Sugar					X
Protein	X	X	X		
Calcium	X				
Phosphorus	X		X		
Iron		X	X		
Vitamin A	X			X	
Thiamin			X		
Niacin		X	X		
Riboflavin	X				
Ascorbic acid				X	

*Food group mentioned provides 20% or more of the constituent in question.

intakes were higher than recommendations.[31,32] Finally, preliminary estimates from the HANES data indicate that the intakes of both children and adolescents of these ages are higher in total fat, saturated fat, added sugar, protein, and sodium than the levels specified in the *Dietary Goals*.[33] We can conclude that the present dietary patterns of many children and adolescents deviate significantly from whatever recommendations one wishes to use.

Tables 1 and 2 present the dietary intakes of children 6 to 11 and adolescents 12 to 17 years of age from the HANES survey data by groups of foods consumed. The proportion of total calories from each food group and the contributions that exceed 20% of total intakes for each of the other nutrients specified are listed. A glance at the tables will illustrate the reason why rather specific information on food choices must be provided if one is to devise diets that meet the dietary goals and fulfill recommended allowances. Note that the "milk" and "meat" groups that have traditionally been emphasized as being the mainstays of children's diets because they make generous contributions of protective nutrients are "problem" foods from the standpoint of their rather large contributions to total fat, saturated fat, and cholesterol. Another old favorite of nutrition educators and pediatricians, the bread and cereal group, makes substantial contributions to sodium intakes and provides many of the protective nutrients. The fruit and vegetable group provides relatively little of any of these substances, but is a good source of vitamin A, some of the B vitamins, folic acid, and ascorbic acid. The final food group in these tables, eg, the "fats, sweets, alcohol" group, provides a good deal of fat, sugar, and energy, but contributes almost none of the protective nutrients.

Table 3.—Suggestions to Parents for Cutting Back on Fat in Family Diets

1. Cut down on fatty meats such as regular ground beef, corned beef, spareribs, sausage, heavily marbled cuts of beef such as prime ribs and steak. Leaner cuts of red meat include flank, round, and rump (especially choice or good rather than prime grades), lamb legs and loin, lean ham and lean pork loin, picnic and Boston butt hams.
2. Broil or bake rather than fry. Trim meat of fat before eating.
3. Substitute lower fat meats such as veal and poultry in place of fatty meats. Use fish and legumes more frequently.
4. Substitute low-fat or nonfat skim milk for whole milk, and low-fat for high-fat dairy products. This implies reduction in the use of whole milk and milk products such as most cheeses and ice cream, and substitution of lower fat products such as skim milk, uncreamed cottage cheese, low-fat yogurt and low-fat cheeses.
5. Instead of table fats like butter, use polyunsaturated "soft" margarines, which are lower in saturated fat.
6. Decrease consumption of hidden sources of fats present in fried foods, foods served with heavy sauces or gravies, baked goods such as pastries, chocolate, nuts, and "regular" peanut butter (natural peanut butters are somewhat lower in fat and sugar).

Table 4.—Suggestions to Parents for Cutting Back on Sugar in Family Diets

1. Keep the sugar bowl off the table.
2. Decrease candy, pie, pastry, cake, cookie, and sweet roll consumption. Save them for weekends.
3. Avoid desserts or between-meal snacks of sweet, sticky foods.
4. Avoid regular soft drinks, punches, fruit drinks, and ades high in sugar. Fruit juices contain less sugar.
5. Buy fruit canned in its own juice or in light instead of heavy syrup (which is also high in sugar), or eat fruits raw.
6. Check ingredient labels. Avoid those that have sugar (or words that mean sugar, such as glucose, sucrose, fructose, corn syrup, or sweeteners) high on the ingredient list.
7. Avoid presweetened products.

RATIONALE

The rationale of the menu planning approach described herein rests on several assumptions that need to be understood by parents if they are to use these diets for their children. First, the most appropriate way to assure sufficiency while avoiding an excess of nutrients or energy is to alter the type and amounts of foods individuals in these age groups commonly eat. The use of vitamin or mineral supplements is not regarded as necessary if the steps outlined are followed. However, children eat most of their food at home and copy the habits of their parents; and it is unreasonable to expect that children will follow dietary patterns that are radically different from those of their families. Therefore, changes in food availability in the home and eating habits of the entire family, and not only those of the child, will be necessary. General suggestions are provided in Tables 3 to 5, and the menus provided are suitable for adults as well as children with minor modifications.

Second, eating should be pleasant. Children have a right to a certain amount of independence in their own food choices. Diets should be flexible enough to permit individual choice and variety, and be adaptable to the child's individual social life.

Third, the menus presented herein are suitable only for well children over 5 years of age or for adults. They provide less calcium, phosphorus, iron, and zinc than recommended levels for younger children. Nor are they suitable as substitutes for therapeutic diets. Expert assistance from a physician and a dietitian is called for if diets for children or adolescents who fall into these categories are to be developed.

Fourth, health promotion measures other than diet also are seen as important. Diet is only one of the health promotion and disease prevention measures appropriate for children and adolescents. Adequate exercise, good sense in using food for rewards or other emotional purposes, oral hygiene, and regular health care are also indicated. It is within this general context that nutrition education should be provided.

Fifth, vegetarian diets are not called for. Some parents and physicians have become confused and assume that since the micronutrient levels suggested are more similar to vegetarian patterns than are current American diets that a switch to vegetarianism is necessary. This is actually not the case—modifications can be achieved simply by moderation in the use of some types of animal foods. Actually, vegetarian patterns usually

Table 5.—Suggestions to Parents for Cutting Back on Salt in Family Diets

1. Keep the salt shaker off the table.
2. Cut back on salting foods during cooking; use lemon juice, herbs, and spices instead.
3. Cut down on salty snacks such as potato chips, pretzels, salted popcorn, salted nuts, and crackers.
4. Avoid salty and smoked meats and fish like bologna, corned beef, chipped beef, frankfurters, ham, luncheon meats, salt pork, sausage, smoked tongue, salt or dried cod, herring, and anchovies.
5. Cut down on other high-salt foods such as processed cheese, aged cheese, foods prepared in brine (pickles, olives, sauerkraut), canned and instant soups or bouillons, oriental noodles with soup, garnishes and condiments like soy sauce, Worcestershire sauce, mustard, and barbecue sauce.
6. Check food labels and avoid foods in which sodium or salt is high on the ingredient list.

provide less animal protein, sugar, total fat, saturated fat, sodium, and cholesterol than do the dietary goals.[34-36] Some of the more restrictive vegetarian regimens include additional constraints on the use of foods that are considered to be "processed" or "nonorganic" (such as some fortified and enriched foods), and disuse of vitamin and mineral supplements. Such practices increase the difficulties of achieving sufficiency for some micronutrients. Those who wish to counsel patients on following vegetarian diets are referred to several excellent references on planning of vegetarian regimens.[37-39]

SPECIFIC RECOMMENDATIONS

Diet Strategy

In order to help parents plan diets that achieve these objectives, this five-point strategy is helpful.

1. *Decrease choices of foods such as fats, sugars, and sweets that contribute a great deal of energy, fat, or sugar, and little else. Substitute foods that are more balanced in their contributions.*

In making suggestions to parents, foods that are high in energy and low in protective nutrients are the first to tackle and cut back on. There are three reasons for "going easy" on choices in this group. First, this group constitutes almost a quarter of overall energy intakes in children's diets. Second, most of the commonly eaten items in this group provide disproportionately high amounts of energy for their contributions of protective nutrients. If energy intakes are excessive, cutbacks on energy contributions from these sources will do little violence to overall diet quality and may, in fact, help to improve it. Third, this group also contributes a substantial proportion of the total fat and sugar (and especially the sticky, sugary foods eaten between meals that particularly increase risks of dental caries development) in children's diets. Dietary alterations specified in Tables 3 and 4 can help in achieving these objectives.

Theoretically, it might seem sensible to simply tell parents to eliminate these items entirely from their diets and those of their children. But such a strategy is doomed to failure. These foods are widely available and highly preferred by everyone in the family. They are often used for emotional purposes since they are regarded as "fun" foods, treats, or rewards. Therefore, the proper strategy is to decrease their intake but not eliminate them, while providing acceptable substitutes.

If children take lunch or a snack to school, parents should pack suitable snack and dessert items that are lower in calories and fermentable carbohydrates, using the lists given in Table 6. Children need a good deal of assistance in making wise choices of snacks, "treats," or desserts eaten outside of the home, since sugary, sticky candies and confections are popular. Suggestions given in Tables 4 and 6 may also be helpful for this.

2. *Increase consumption of fruits and vegetables, breads and cereals, dried beans or peas, and starchy vegetables.*

• **Fruits and Vegetables.**—Taken together, fruits and vegetables, including juices, make only minor contributions to total calories. As a group, they are low in calories and high in protective nutrients such as ascorbic acid, vitamin A value, and folic acid, provide a good deal of dietary fiber, and contribute less than their proportion of calories for all of the food constituents mentioned in the guidelines except for sugar, which appears primarily as a natural constituent in some fresh fruits. Starchy vegetables such as potatoes and corn are also relatively low in calories and are filling.

Fruits are highly acceptable substitutes for sweets and the usual desserts and snacks, which are higher in sugar and calories. Their consumption should be stressed—at least five or more servings a day. At least one good ascorbic acid source and a dark green or deep yellow vegetable for vitamin A should be included each day among selections from this group.

• **Whole Grain, Enriched or Fortified Cereals, and Bread.**—In their totality, this group constitutes about a quarter of total calories. With the exception of sodium, they make only minor contributions of constituents for which greater moderation is called for (fat, saturated fat, cholesterol, and sugar), while providing relatively large amounts of the protective nutrients (iron, protein, several of the B vitamins, and complex carbohydrates). Whole grain products are also rich in magnesium, trace elements, folic acid, and fiber. Fortified cereal products such as breakfast cereals usually have increased levels of iron and may also contain vitamins A, B_{12}, C, and D, not usually present in cereals. Enriched products provide amounts of iron, thiamin, riboflavin, and niacin similar to those in whole grain products. For this reason, whole grain, enriched, or fortified foods from this group should be emphasized rather than the highly refined, unfortified products.

The strategy is to increase consumption of whole grain or enriched breads, whole grain, enriched and fortified cereals (especially the unsugared varieties), and other low-fat cereal products. Some are good snack choices. The mixed protein dishes, such as casseroles, can be used as entrees, while others are good side dishes. Four to six servings of these foods a day are suggested.

• **Dried Beans, Peas, and Nuts.**—Foods such as soybeans, baked beans,

Table 6.—Snack Foods That Are More Acceptable Substitutes Than Usual Choices for Children and Adolescents

1. Fresh fruits or water-packed canned fruits.
2. Finger vegetables such as radishes, carrot sticks, celery stalks, and raw cauliflower pieces, and cherry tomatoes.
3. Fruit juices.
4. Low-fat yogurt (unsweetened).
5. Low-fat or skim milk.
6. Low-fat cheese.
7. Nuts or sunflower seeds.
8. Whole grain or enriched crackers (unsalted).
9. Unsalted popcorn or pretzels.

peanuts, lentils, and other types of dried beans and peas are high in protein, phosphorus, vitamin B_6, and magnesium, while being lower in energy and saturated fat than many animal foods that are also high in these nutrients. Therefore, their use should be encouraged.

3. *Substitute alternatives for whole fat milk products, fatty meats, and eggs that are lower in energy, lower in fat, saturated fat, cholesterol, and sodium, while keeping protective nutrient contributions of foods in these groups at a high level.*

Since these foods make major contributions of protective nutrients, the strategy in dealing with them is to exchange or substitute similar foods that have these advantages and also are lower in total fat, saturated fat, cholesterol, or sodium.

• **Whole Fat Milk Products.**—Milk and milk products provide almost a quarter of the total calories children eat. While they make substantial contributions of calcium, phosphorus, vitamins A, D, B_2, and protein, they also provide a good deal of the total fat, saturated fat, cholesterol, and sodium, as well as a fair amount of sugar in children's diets. By one simple measure, substituting vitamin D-fortified skim milk for whole milk, total fat, saturated fat, and energy can be substantially reduced while preserving intakes of the protective nutrients. This is probably the simplest single recommendation that can be given to parents. Most children are accustomed to the taste and rich mouth feel of whole milk, and so a gradual "weaning" process, rather than an out-and-out switch, is sensible. By mixing reconstituted skim milk from powder in equal proportions with whole milk, homemade 2% milk can be easily produced at a substantial savings over usual fluid milk costs. Gradually, the ratio can be increased to two parts skim to one part whole milk, and the result is a nearly skim milk with slightly more body and lower cost than store-bought skim milk. Low-fat cheeses and sherbet or ice milk instead of ice cream are also in order here. At least three servings from these foods should be included each day.

• **Fatty Meats.**—Meats contribute about an eighth of total calories and provide substantial proportions of protein, iron, niacin, and vitamins B_6 and B_{12}. However, some items, such as fatty red meats, provide relatively more total fat, saturated fat, and cholesterol than their caloric contribution. The strategy here is to emphasize more consumption of poultry, fish, shellfish, legumes (beans, peas), and nuts, which are lower in fat and cholesterol. At the same time, the use of trimmed or lower fat cuts of red meats should be encouraged.

In food preparation, a balance of about half meat and half poultry, fish, or low-fat meats can be aimed for. Broiling and baking are preferable to frying. Meats should be trimmed before eating and drippings should be discarded. At least two servings of fish, poultry, lean meat, or dried beans should be included each day.

• **Eggs.**—Eggs are good sources of protein and also provide substantial amounts of vitamin A. However, an average egg provides approximately 250 mg of cholesterol, and thus it is also a major contributor to dietary cholesterol. There is no reason to eliminate eggs from children's diets since their current intakes do not appear to be excessive.

4. *Help parents make changes that will facilitate this dietary pattern.*

Importance of Parents as Role Models.—Many parents are unaware of the great influence their own eating behavior has on that of their children. They should be encouraged to alter their own diets to serve as better role models for their children.

Altering Food Availability in the Home.—The key to modifying children's and adolescents' diets is for the shopper to buy and stock home larders with appropriate foods. Food preparation practices also need alteration, and these depend more on the parent than they do on the child. Helpful alterations include choices of lean meats, poultry, and fish; the trimming of fatty meats; draining of drippings; use of broiling and baking rather than frying; disuse of salt in food preparation and on the table; use of soft margarines or vegetable oils in cooking and as table spreads; providing easy access to fruits, vegetables, and juices for snacks and desserts.

Parental Views Should Be Publicized for Food Variety to Be Available Away From Home.—All too often, parents assume that they have no influence over what their children eat in schools, recreation centers, and so on, but in many of these settings, such as schools, means do exist whereby parents can urge that alternative choices be provided. Parents should be encouraged to become involved in advisory groups and boards that make these decisions so that school lunches and other meals children are likely to eat outside the home can be adjusted to meet children's diets.

Pack Suitable Lunches and Snacks.—Contrary to myth, children obtain many of the sugary sweets, desserts, confections, and beverages they eat in their own homes or in home-packed lunches that they take to school. Table 3 suggests some appropriate substitutes for the usual snacks and desserts that are used in many packed lunches for children.

Assist Children in Making Wise Choices When Eating Away From Home.—Parents need to teach children to make wise food choices when children are on their own. Helpful guides are available to help them do this.[6,40]

5. *Assure adequate attention to oth-*

Table 7.—Menus for Children and Adolescents That Approximate Dietary Goals

Breakfast	Lunch	Dinner	Snacks
Iron-fortified wheat cereal, 1 cup Sugar, 1 tsp Banana, 1 Milk, skim, 1 cup	Cheeseburger and bun Coleslaw, 1/2 cup French fries, 1 serving Milk, skim, 1 cup	Chicken cacciatore, 1 serving Spaghetti, 1 cup Escarole, 1/2 cup, braised Tossed salad, 1-½ cup Italian dressing, 1 Tbsp Italian bread, 2 slices Margarine, 1 tsp, soft Tangerine, 1 medium Milk, skim, 1 cup	Peanut butter–orange sandwich (2 slices whole wheat bread, orange slices, peanut butter) Milk, skim, 1 cup Soft drink, 8 oz
Orange juice, 3/4 cup Scrambled egg, 1 large Bagel, 1 Neufchatel (low-fat cream cheese), 1 Tbsp Milk, skim, 1 cup	Chicken sandwich (3 oz white meat, 1 tsp soft margarine, 1 tsp salad dressing, 2 slices whole wheat bread) Raw green pepper, 1, sliced Apple, 1 medium Milk, skim, 1 cup	Vegetable chowder, 1 serving Bean salad, 1 serving Baked fish, 1 serving Broccoli, 1/2 cup Brown rice, 1/2 cup Rye bread, 2 slices Margarine, 2 tsp, soft Honeydew melon, 1 slice Milk, skim, 1 cup	Gingerbread, 1 slice Applesauce, unsweetened, 1/2 cup, and cinnamon sandwich with 2 slices whole wheat bread 1 orange Milk, skim, 1 cup
Raisin-type English muffins, 2 Peanut butter, 2 Tbsp Cantaloupe, 1/4 medium Milk, skim, 1 cup	Pork loin, 1 large, lean only Carrots, 1/2 cup Black-eyed peas, 1/2 cup cooked Rice, 1/2 cup Sliced peaches, 1/2 cup Milk, skim, 1 cup	Flounder, 1 serving Mashed potato, 1/2 cup, with margarine Broccoli, 1/2 cup Whole wheat roll, 1 Margarine, 2 tsp, soft Low-fat plain yogurt, 1 cup Blueberries, 1/2 cup Milk, skim, 1 cup	Corn muffins, 2 average Jelly, 2 Tbsp Apple cider, 3/4 cup Raw vegetable sticks, 1/2 cup
Orange juice, 3/4 cup Banana-nut bread, 3 slices Cottage cheese, low-fat, 3/4 cup Milk, skim, 1 cup	Peanut butter and raisin sandwich Carrot, 1 large Pear, 1 large Milk, skim, 1 cup	Pot roast, lean chuck only, 4 oz Mashed potato, 3/4 cup Green beans, 1/2 cup Spinach salad, 1 cup Italian dressing, 1 Tbsp Biscuits, 2 Margarine, 2 tsp, soft Ambrosia, 1/2 cup Milk, skim, 1 cup	Chili bean dip Raw vegetable sticks, 1 cup Whole wheat crackers, 6 Apple, 1 medium Milk, skim, 1 cup with chocolate syrup, 1 Tbsp
Fresh grapefruit, 1/2 medium Shredded-wheat biscuits, 2 Sugar, 1 tsp Milk, skim, 1 cup	Turkey-ham sandwich on rye bread (2 oz turkey, 1 oz ham, and 2 slices rye bread) Margarine, 2 tsp Pear, 1 medium Milk, skim, 1 cup	Green salad, 1 cup French dressing, 2 Tbsp Chopped steak, 4 oz Acorn squash with 1 tsp brown sugar, 1/2 medium Green beans, 1/2 cup Corn bread, 1 serving Baked apple with 2 tsp brown sugar, 1 medium Milk, skim, 1 cup	Orange-pineapple juice, 3/4 cup Peanut butter sandwich (2 Tbsp peanut butter and 2 slices whole wheat bread) Milk, skim, 1 cup Celery sticks Swiss cheese cubes, 1-½ oz
Orange juice, 3/4 cup Whole wheat pancakes, 3 Maple syrup, 2 Tbsp Margarine, 2 Tbsp, soft Milk, skim, 1 cup	Beef tacos, 2 Tossed salad (lettuce, tomato, green onions, and carrots), 1-¼ cup Italian salad dressing, 1 Tbsp Milk, skim, 1 cup	Roast loin of pork, lean only, 4 oz Sweet potato, baked, 1 medium Cauliflower, 1/2 cup Biscuits, 2 Margarine, 2 Tbsp, soft Honey, 1 Tbsp Fresh fruit cup (oranges, apples, banana), 2/3 cup Milk, skim, 1 cup	Graham crackers, 4 Apple, 1 medium Lemonade, 12 oz
Orange-grapefruit juice, 3/4 cup Oatmeal with cinnamon and 2 Tbsp raisins, 1/2 cup Brown sugar, 1 tsp Milk, skim, 1 cup	Pea soup, 1 serving Chicken-salad sandwich on rye bread (2 oz chicken, 1 Tbsp celery, 1 tsp onion, 2 Tbsp mayonnaise) Tomato, 1 whole Margarine, 2 Tbsp, soft Plum, 1 Milk, skim, 1 cup	Beef with Chinese vegetables, 1-½ servings Brown rice, 1 cup Pineapple chunks, canned, 1/2 cup Milk, skim, 1 cup	Banana-nut bread, 2 slices Lemon sherbet, 1/2 cup Apple, 1 Apple crisp, 1 serving

er health-promotive life-style behaviors closely related to diet.

Encourage Vigorous Physical Activity.—Americans are among the most sedentary people in the world, and their children are no exception. There are a number of reasons for encouraging both children and their parents to lead more physically active lives, regardless of whether they are lean or fat. First, the more active the child, the more food he or she will eat and the easier it is to assure that protective nutrient needs are met. Those who eat diets providing relatively little energy, even if their weights are within normal limits, often have low intakes of iron, vitamin B_6, zinc, and magnesium. Second, it is easier to maintain normal fatness status or, if necessary, to reduce it if the child regularly engages in vigorous physical activity. Third, there is reason to suspect that, at least in adults, vigorous physical activity as well as diet and nonsmoking is associated with elevated levels of high-density lipoproteins, which may be associated with a lowered risk of coronary heart disease later in life.[41,42] While this chronic degenerative disease is not an immediate problem for most children, the habit of exercise and weight control inculcated in childhood can be helpful in decreasing risk of disease later in life. A fourth reason for encouraging vigorous physical activity is that it may decrease stress or emotionally related eating by furnishing something else to do in its place. The point here should be to stress a physical activity program and not simply exercise. Activity and exercise both are necessary to raise children's energy outputs.[43-46]

Oral Hygiene.—Frequent toothbrushing, swishing, and the use of dental floss and fluoridated water or supplements, regular dental care, as well as food choices low in retentive, fermentable carbohydrates also need to be stressed to ensure dental health.

Alcohol Use.—The use of alcohol is obviously to be discouraged in diets of individuals of these ages. However, surveys indicate that a sizeable proportion of adolescents drink alcoholic beverages and that more and more do so as they reach the third decade of life. Therefore, sensible advice about moderation in drinking is in order.

Table 8.—Nutrients Provided in Menus in Table 7 per Day

Nutrient	Menus (Table 7)	Intakes per Day: Children 6-11 yr RDA†	Children 6-11 yr Present Intakes (Mean)	Adolescents 12-17 yr RDA†	Adolescents 12-17 yr Present Intakes (Mean)
Calories	2,722	2,400	2,026	2,800	2,271
Protein, g	132	34	75	56	85
Vitamin A, μg retinol equivalents	3,656	700	636	1,000	590
Vitamin D, μg	430	10	...	10	...
Vitamin E, mg α-tocopherol equivalents	?	7	...	10	...
Vitamin C, mg	204	45	81	60	84
Thiamin, mg	2.2	1.2	1.3	1.4	1.4
Riboflavin, mg	2.8	1.4	2.1	1.7	2.2
Niacin, mg niacin equivalents	30.0	16	14	18	17
Vitamin B_6, mg	2.5	1.6	...	2.0	...
Folacin, μg	316	300	...	400	...
Vitamin B_{12}, μg	6.9	3.0	...	3.0	...
Calcium, mg	1,760	800	910	1,200	960
Phosphorus, mg	2,252	800	1,283	1,200	1,346
Magnesium, mg	499	250	...	400	...
Iron, mg	23	10.0	11.0	18.0	12.0
Zinc, mg	18	10.0	...	15.0	...
Iodide, μg	?	120	...	150	...
Fat, % of calories	30	30	37	30	37
Saturated	~9	10	13	10	13
Monounsaturated	~11	10	...	10	...
Polyunsaturated	~10	10	...	10	...
Carbohydrate, % of calories	51	58	49	58	48
Complex and naturally occurring sugars	?	48	...	48	...
Refined and processed sugars	~8	10	...	10	...
Protein, % of calories	19	12	15	12	15
Cholesterol, mg	306	300	187	300	312
Sodium, mg	2,969	2,000	2,378	2,000	2,464

*Compared with 1979 recommended allowances, dietary goals, and present mean intakes of children and adolescents from the Health and Nutrition Examination Survey.
†RDA indicates recommended daily allowance—highest value for age-sex categories.

Examples of Menus

Table 7 provides a week's worth of menus that illustrate the types of dietary alterations that are called for if one wishes to feed children diets that approximate both the recommended allowances and the dietary goals. Table 8 shows the nutrients provided per day for the week's worth of menus and contrasts these to the relevant recommendations for children and adolescents. These menus meet the recommended allowances and also come quite close to the *Dietary Goals* for the United States (second edition) in most respects.[4] For children, and especially for adolescent girls, it is important to emphasize the use of skim milk to ensure that needs for calcium and vitamin D are met during periods of rapid growth. Girls, especially in late adolescence, may choose to use more liberal amounts of iron-fortified cereals for breakfast or whole grain and enriched cereal products to ensure that recommended allowances for iron and zinc are met. Young women also need to make a deliberate effort to keep their energy outputs up since this will permit them to eat more food (and more of these nutrients) while staying in energy

balance. For example, for those few girls of this age who are in energy balance at 2,400 calories, most of the recommended allowances would be met. However, at low levels of energy intake (eg, 1,800 calories), vitamins B_6, folic acid, and the minerals calcium, iron, and zinc would be in short supply.

Other points to emphasize are that salting of foods at the table should be discouraged, and that if sugary candies or confections are eaten, desserts included at meals should be eschewed. Children who consume less than 2,400 calories per day can be fed from these menus by decreasing the portion sizes provided; those who eat more can be fed by increasing the sizes.

Some children and adolescents prefer to eat light lunches, while others eat school lunches that provide ample (eg, one third of the recommended daily allowances) amounts of food. Either pattern can be compatible with good nutrition as long as it is kept in mind that the quality of snacks and foods eaten between meals is also important, and by the end of the day choices should approximate the food groups specified in the menus.

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The menus presented in Table 7 are adapted from similar menus planned and calculated for adults by Frances Cronin, RD, PhD, Luise Light, EdD, Nancy Gaston, MS, Margaret Mitchell, MPH, and Susan Krebs, MPH, working under the direction of D. M. Hegsted, PhD, of the Human Nutrition Center, Science and Education Administration, US Department of Agriculture. Mary Mead, RD, MEd, and Carol Stollar, RD, MEd, of the Frances Stern Nutrition Center, offered assistance in revising menus to child tastes. Andrea Scarpa and Glenda Brown typed the manuscript. Candice Gibson, PhD, performed the calculations of the menus. The author accepts full responsibility for statements, calculations, and conclusions reached.

References

1. General Mills Inc: *A Summary Report on US Consumer Knowledge, Attitudes and Practices About Nutrition.* Minneapolis, General Mills Inc, 1976.

2. Yankelovich, Skelly & White, Inc: *Family Health in an Era of Stress: The General Mills American Family Report 1978-79.* Minneapolis, General Mills Inc, 1979.

3. Dwyer JT, Alston E: Nutrition in family life. *Food Product Dev* 10:44-47, 1976.

4. Select Committee on Nutrition and Human Needs, US Senate: *Dietary Goals for the United States,* ed 2. Washington, DC, US Government Printing Office, 1977.

5. *The Surgeon General's Report on Health Promotion and Disease Prevention: Healthy People.* US Dept of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health and Surgeon General, DHEW (PHS) Publication No. 79-55071, US Government Printing Office, 1979, pp 33-52 and 131.

6. US Dept of Agriculture: *Food.* Washington, DC, US Government Printing Office, 1979.

7. US Dept of Agriculture and Health, Education, and Welfare: *Nutrition and Your Health: Dietary Guidelines for Americans.* Washington, DC, US Government Printing Office, 1979.

8. Page L, Phipard E: Essentials of an adequate diet: Facts for nutrition programs. USDA Home Economics Research Report 3, 1957.

9. US Dept of Agriculture: *Food for Fitness: A Daily Food Guide.* USDA Leaflet No. 424, Washington, DC, March 1958.

10. Hertzler AA, Anderson HL: Food guides in the US. *J Am Diet Assoc* 64:19-22, 1974.

11. Ahlstrom A, Rasanen L: Review of food grouping systems in nutrition education. *J Nutr Ed* 5:13-17, 1973.

12. Foman SJ: *Nutritional Disorders of Children: Prevention, Screening and Follow-up,* DHEW Publication HSA 76-5612, US Dept of Health, Education, and Welfare, Public Health Service, Health Services Administration, 1976.

13. Peterkin BB, Kerr RI, Shore CJ: Diets that meet the dietary goals. *J Nutr Ed* 10:15-21, 1978.

14. Peterkin BB, Shore CJ, Kerr EI: Some diets that meet the dietary goals for the US. *J Am Diet Assoc* 74:423-439, 1979.

15. Latham MC, Stephenson LS: For the US dietary goals. *J Nutr Ed* 9:152-153, 1977.

16. Harper AC: Against the US dietary goals. *J Nutr Ed* 9:154-156, 1977.

17. Harper AE: Dietary goals: A skeptical view. *Am J Clin Nutr* 31:310-315, 1978.

18. Hegsted DM: Dietary goals: A progressive view. *Am J Clin Nutr* 31:1504-1509, 1978.

19. Leveille GA: *Establishing and Implementing the Dietary Goals: Family Economics Review,* USDA Publication ARS-NE 36, 1979, pp 7-11.

20. Hegsted DM: Priorities in nutrition in the United States. *J Am Diet Assoc* 71:9-12, 1977.

21. Hegsted DM: Rationale for change in the American diet. *Food Tech* 32:44-48, 1978.

22. Reiser R: Oversimplification of diet—coronary heart disease relationships and exaggerated diet recommendations. *Am J Clin Nutr* 31:865-872, 1978.

23. Olson RE: Are professionals jumping the gun in the fight against chronic disease? *J Am Diet Assoc* 74:543-547, 1979.

24. Ahrens EH, Connor WE (eds): Symposium report on dietary factors relating to the nation's health. *Am J Clin Nutr* 32:2627-2631, 1979.

25. Olson RE: Response to dietary goals for the US: Eggs, in US Senate Select Committee on Nutrition and Human Needs: *Diet Related to Killer Disease.* Washington, DC, US Government Printing Office, 1977, vol 6, pp 7-10.

26. Simopoulous A: The scientific basis for the 'goals': What can be done now? *J Am Diet Assoc* 74:539-542, 1979.

27. Weil WB: National dietary goals: Are they justified at this time? *Am J Dis Child* 133:368-370, 1979.

28. Woodruff C: Dietary goals for the United States. *Am J Dis Child* 133:369-370, 1979.

29. US Dept of Health, Education, and Welfare: *Ten State Nutrition Survey, 1968-70, Highlights.* US Dept of Health, Education, and Welfare, Health Services and Mental Health Administration, Center for Disease Control, US Government Printing Office, 1972.

30. National Center for Health Statistics: *Caloric and Selected Nutrient Values for Persons 1-74 Years of Age: First Health and Nutrition Examination Survey 1971-74.* Vital and Health Statistics Series 11, No. 209. DHEW Publication (PHS) 79-1657, US Dept of Health, Education, and Welfare, Public Health Services, Office of Health Research Statistics and Technology, National Center for Health Statistics, Hyattsville, Md, June 1979.

31. National Center for Health Statistics: *Height and Weight of Youths Ages 12-17 Years in the United States: National Health Survey.* Vital and Health Statistics Series 11, No. 124. DHEW Publication (HSM) 73-1606. US Dept of Health, Education, and Welfare, Public Health Services, Health Resources Administration, National Center for Health Statistics, Rockville, Md, January 1973, p 9.

32. Garn SM, Clark DC: Trends in fatness and origins of obesity. *Pediatrics* 57:443-446, 1976.

33. Abraham S: Fat, cholesterol, and sodium intake in the diet: United States. Read before the USDA's BARC Symposium—Human Nutrition, Beltsville, Md, May 5, 1979.

34. Dietz WH, Dwyer JT: Nutritional implications of vegetarianism in children, in Suskind R (ed): *Pediatric Nutrition.* New York, Raven Press, 1980.

35. Committee on Nutrition Misinformation, Food and Nutrition Board, National Research Council: Vegetarian diets. *J Am Diet Assoc* 65:121-124, 1973.

36. Register UD, Sonnenberg LM: Scientific and practical considerations of the vegetarian diet. *J Am Diet Assoc* 62:253-257, 1973.

37. Seventh-Day Adventist Dietetic Association: *Utilizing a Vegetarian Diet Plan,* ed 5. Loma Linda, Calif, Seventh-Day Adventist Dietetic Association, 1978.

38. New York City Department of Health: *The Vegetarian Follows the Starguide to Food Eating: A Guide to Vegetarian Eating.* New York, Bureau of Nutrition, New York City Department of Health, 1976.

39. Vhymeister IB, Register UD, Sonnenberg LM: Safe vegetarian diets for children. *Pediatr Clin North Am* 24:203-210, 1977.

40. US Dept of Agriculture: *What's to Eat? And Other Questions Kids Ask About Food.* USDA Yearbook of Agriculture, 1979, Washington, DC, US Government Printing Office, 1979, Stock No. 001-000-04041-3.

41. Gordon T, Castelli WP, Hjortland MC, et al: High-density lipoprotein as a protective factor against coronary heart disease. *Am J Med* 62:707-714, 1977.

42. Harking GH, Foreyt JP, Mitchell RE, et al: Relation of diet to high-density lipoprotein cholesterol in middle age in marathon runners, joggers and inactive men. *N Engl J Med* 302:357-361, 1980.

43. Seltzer CC, Mayer J: An effective weight control program in a public school system. *Am J Public Health* 60:674, 1970.

44. Dwyer JT, Mayer J: A preventive program for obesity control: Five-year follow-up on success of an educational endeavor to influence physical activity and diet among 13-year-old girls, in Burland WL, Samuel PD, Yudkin J (eds): *Obesity.* New York, Churchill-Livingstone, 1974.

45. Dwyer JT: Patient oriented perspectives on management of obesity related problems of adolescents, in Tobin RB, Mehlman M (eds): *Advances in Modern Nutrition.* Park Forest South, Ill, Pathotox Publishers, 1980.

46. Bray GA: *Obesity in America.* US Dept of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication 79:359, 1979.

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Hypersensitivity to Eggs, Chicken, or Chicken Feathers: For measles- and/or mumps-containing vaccines, in patients hypersensitive to eggs, chicken, or chicken feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions.

Pregnancy: *ATTENUVAX*—The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.
Vaccine administration to postpubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of postpubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception that ATTENUVAX, MUMPSVAX, and/or MERUVAX II may be administered simultaneously. BIAVAX II may be administered simultaneously with ATTENUVAX. Monovalent or trivalent poliovirus vaccine, live, oral, may be administered simultaneously with ATTENUVAX and/or MUMPSVAX. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. However, rubella vaccine may be given prior to discharge to susceptible postpartum patients who received blood products, provided that a repeat HI titer is drawn six to eight weeks after vaccination to insure seroconversion; similarly, although rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_0 (D) immune globulin (human) without interfering with vaccine effectiveness, a follow-up postvaccination HI titer should also be determined.
Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines. Vaccination may not result in seroconversion in 100 percent of susceptible subjects.
Measles-Containing Vaccines—Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.
Rubella-Containing Vaccines—Excretion of live attenuated rubella virus from the nose and throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, is not regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.
Measles-Containing Vaccines—Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who previously received killed measles vaccine; the combination vaccines were not given under this condition in clinical trials.
Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5 to 10 cases of SSPE per million cases of natural measles.
Rubella-Containing Vaccines—Adverse reactions include malaise, sore throat, headache, fever, and rash; mild local reactions such as erythema, local pain, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia that is infrequently associated with signs of inflammation, and polyneuritis.
Moderate fever (101–102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.
Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. In children, joint reactions are rare and of brief duration if they do occur. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3 percent; women: 12–20 percent), and the reactions tend to be more marked and of longer duration. Rarely, symptoms may persist for a matter of months. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (35–45 years), these reactions are generally well tolerated and rarely interfere with normal activities.
Mumps-Containing Vaccines—Parotitis and orchitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2–8 C (35.6–46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2–8 C (35.6–46.4 F), and discard if not used within eight hours. Use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.
Color: The color of the vaccine when reconstituted is yellow. ATTENUVAX is acceptable for use only if clear.

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MUMPSVAX® (Mumps Virus Vaccine, Live, MSD)—Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.
Each of these vaccines is supplied as a single-dose vial with a disposable syringe containing diluent and fitted with a 25-gauge, ⅝" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

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Picture of the Month

Sydney S. Gellis, MD, Murray Feingold, MD; Contributed by Charles R. Fikar, MD, Marry Ann Lee, MD

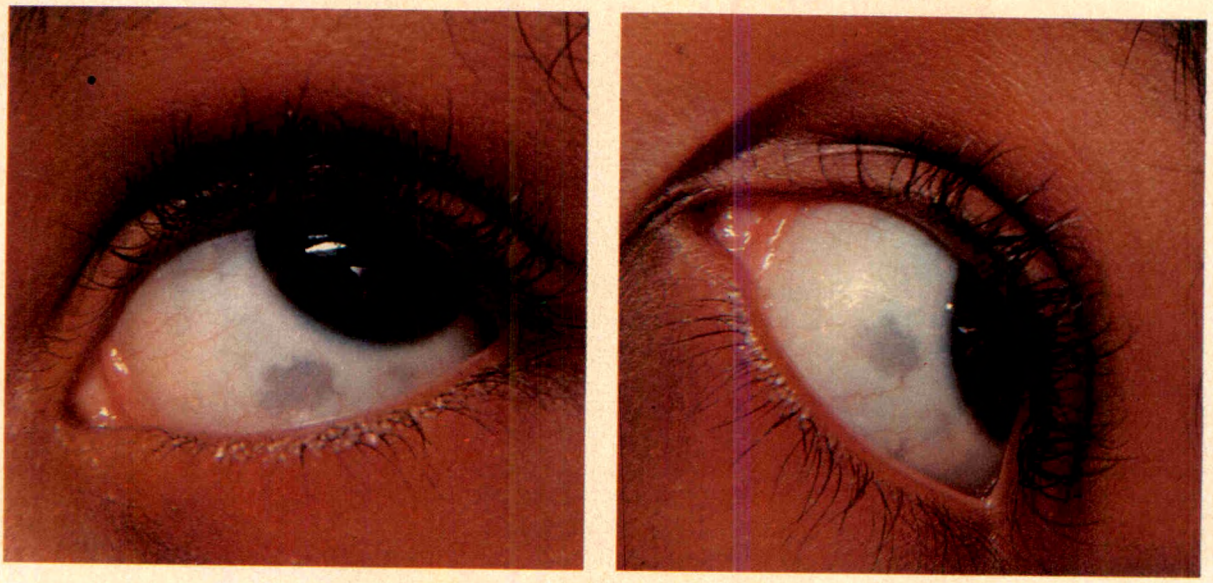

Figure 1.

Figure 2.

From the Department of Pediatrics, University of Rochester, and the Rochester General Hospital, Rochester, NY.

Reprint requests to Boston Floating Hospital, 20 Ash St, Boston, MA 02111 (Dr Gellis).

Denouement and Discussion

Ota's Nevus

Fig 1.—Left, right, Typical macular pigmentation of sclera.

Fig 2.—Hyperpigmentation and discoloration of periorbital skin with almost complete blue "spilt-ink" discoloration of sclera.

Manifestations

Ota's nevus is a disorder of pigmentation characterized by macular lesions that may be tan, brown, slate gray, blue, purple, or black in color and that resemble a mongolian spot in appearance. Involvement is usually unilateral and affects areas innervated by the first, second, and occasionally the third division of the trigeminal nerve.

Approximately two thirds of the patients have scleral involvement ranging from small patchy lesions to an almost completely blue "spilt-ink" staining of the affected eye. Hyperpigmentation of the orbit and associated structures may also occur in the iris, cornea, ocular fundus, optic papilla, retrobulbular fat, periosteum of the orbital bone, or the optic nerve. Glaucoma of the involved eye has been reported.

Other areas of involvement include the mucous membranes of the nose and mouth, tympanic membrane, external auditory canal, neck, and rarely the leptomeninges.

It occurs more commonly in Oriental and black individuals and affects females more commonly than males. The nevus is present at birth in approximately 50% of the patients, and it is noted before age 21 in the majority of the cases. Although these lesions do not disappear, changes in color and shade can occur with age and during menses.

Histologically, dendritic, stellate, and fusiform melanocytes are diffusely scattered in the middle to upper dermis. Transformation into a malignant melanoma occurs in the brain, skin, and eyes and especially the iris. Malignant changes rarely take place in Orientals and blacks but occur in 5% to 15% of the white population with Ota's nevus. Reasons for this are unknown.

Genetics

No specific mode of inheritance has been documented.

Treatment

There is no specific treatment. Bleaching agents are apparently of no avail, but covering cosmetics may be useful. The occurrence, particularly in whites, of malignant transformation warrants periodic ophthalmologic examination.

References

1. Hidano A, Kajima H, Ikeda S, et al: Natural history of nevus of Ota. *Arch Dermatol* 95:187-195, 1967.
2. Lorincz AL: Disturbances of melanin pigmentation, in Moschella ST, Pillsburn DM, Hurley JH (eds): *Dermatology*. Philadelphia, WB Saunders Co, 1975, pp 1104-1105.
3. Sang DN, Albert DM, et al: Nevus of Ota with contralateral cerebral melanoma. *Arch Ophthalmol* 95:1820-1824, 1977.
4. Mohadessan M, Fetkenhour C, O'Grady R: Malignant melanoma of choroid in a case of nevus of Ota. *Ann Ophthalmol* 11:189-192, 1979.

The Editors welcome contributions to "PICTURE OF THE MONTH" *and* "RADIOLOGICAL CASE OF THE MONTH." *Those who wish to contribute should send their manuscripts to Dr Gellis (Picture of the Month), Boston Floating Hospital, 20 Ash St, Boston, MA 02111, or Dr Young (Radiological Case of the Month), Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Radiological Case of the Month

Lionel W. Young, MD; Contributed by Saskia v. W. Hilton, MD, David K. Edwards, MD

From the Department of Radiology, US Naval Regional Medical Center (Dr Hilton), and the Departments of Radiology and Pediatrics, University of California at San Diego (Dr Edwards), San Diego.

Reprint requests to Department of Radiology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr L. W. Young).

A 6-week-old female infant was seen in the outpatient department for a fever of 24 hours' duration. Anteroposterior and lateral supine chest roentgenograms were performed (Fig 1) and the baby was admitted for evaluation of possible sepsis.

Previous medical history and the results of the physical examination were unremarkable. Cerebrospinal fluid via lumbar puncture was consistent with aseptic meningitis. Oblique chest roentgenograms (Fig 2) and a technetium Tc 99m medronate bone scan were obtained. The hospital course was uneventful and the patient was discharged after five days.

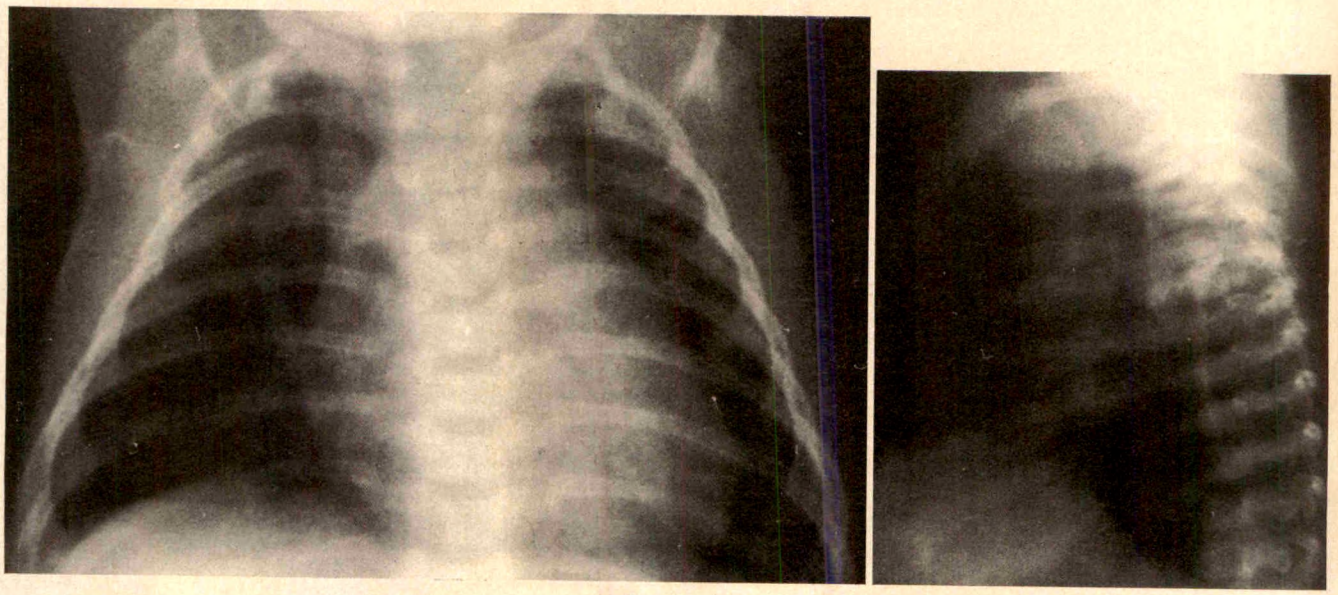

Figure 1.

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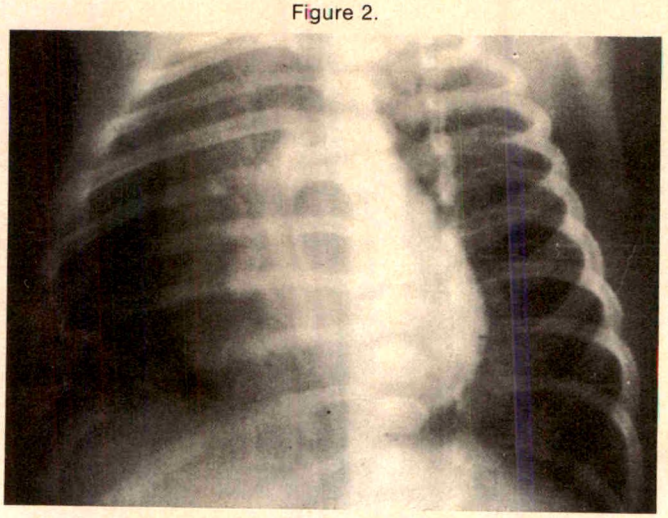

Denouement and Discussion

Intrathoracic Rib

Fig 1.—Left and right, Chest roentgenograms show curved, radiodense structure adjacent to right cardiomediastinal silhouette in anteroposterior view, lying posteriorly in lateral view. Cephalad portion appears to blend with right fourth rib.

Fig 2.—Right posterior oblique view confirms that structure arises from anteromedial aspect of right fourth and fifth posterior ribs and has bony, rib-like appearance. Radionuclide bone scan (not shown) confirmed osseous nature of structure.

Though congenital anomalies of the ribs are common, intrathoracic ribs are extremely rare.[1] They are more frequently seen on the right than on the left and are usually single.[2] Generally, these originate posteriorly and extend downward and slightly laterally to end at or near the diaphragm[1]; in one case, an intrathoracic rib bridged the thorax internally.[3] The rib is always outside the parietal pleura, and the encasing pleural reflection can render the margins of the structure somewhat indistinct and thus hinder diagnosis.[4] However, the diagnosis is facilitated by knowledge of the condition; the structure "looks like a rib,"[5] and, unlike an anomalous vessel, it does not branch.[2] If the bony trabecular pattern cannot be discerned, a radionuclide bone scan is an easy and appropriate method of verifying its osseous nature.

It is important to recognize this structure as an innocuous anomaly so that needless manipulative examinations, and particularly surgery,[4] are not performed.

References

1. Fraser RG, Paré JAP: *Diagnosis of Diseases of the Chest*, ed 2. Philadelphia, WB Saunders Co, 1977, vol 1, p 165.
2. Weinstein AS, Mueller CF: Intrathoracic rib. *AJR* 94:587-590, 1965.
3. Shoop JD: Transthoracic rib. *Radiology* 93:1335-1336, 1969.
4. Plum GE, Hayles AB, Bruwer AJ, et al: Supernumerary intrathoracic rib: A case report. *J Thorac Surg* 34:800-803, 1957.
5. Felson B: *Chest Roentgenology*. Philadelphia, WB Saunders Co, 1973, p 493.

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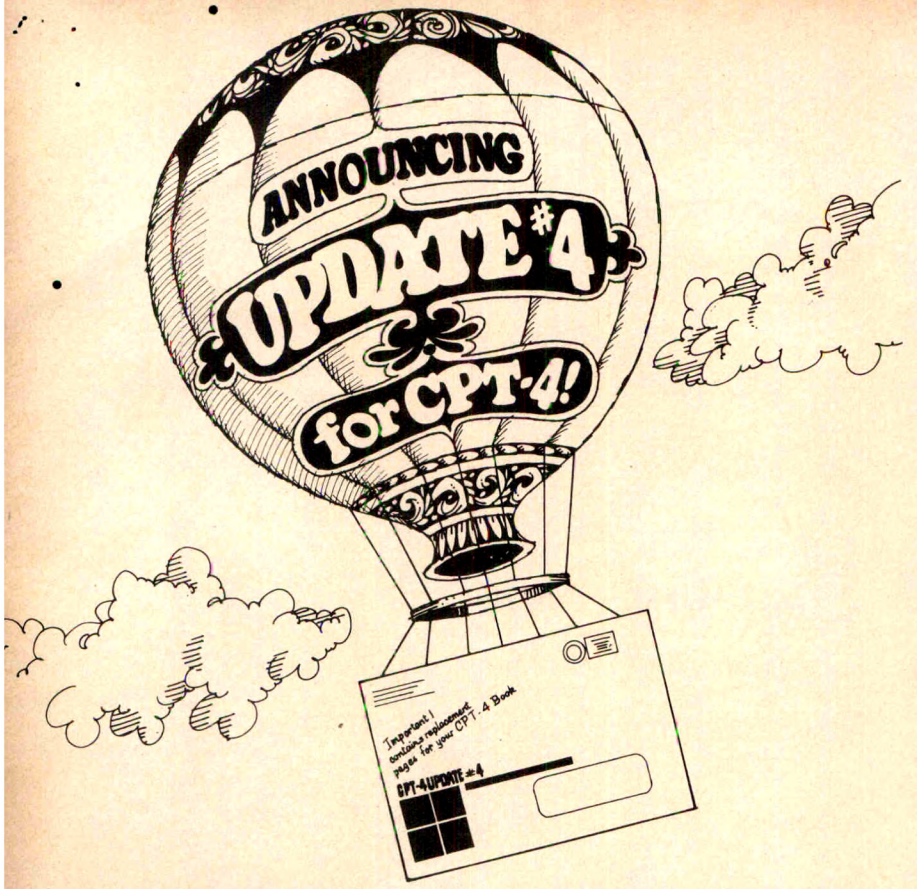

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Staphylococcus aureus – Acute infections of skin and soft tissue which are mild to moderately severe. Resistance may develop during treatment.

S. (Diplococcus) pneumoniae – Infections of the upper respiratory tract (e.g., otitis media, pharyngitis) and lower respiratory tract (e.g., pneumonia) of mild to moderate severity.

Mycoplasma pneumoniae (Eaton Agent, PPLO) – Respiratory tract infections due to this organism.

Haemophilus influenzae – May be used concomitantly with adequate doses of sulfonamides for upper respiratory tract infections of mild to moderate severity. Not all strains of this organism are susceptible at the erythromycin concentrations ordinarily achieved.

Treponema pallidum – As an alternate treatment in penicillin-allergic patients. In primary syphilis, spinal-fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae – As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

C. minutissimum – In the treatment of erythrasma.

Entamoeba histolytica – For intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes – Infections due to this organism.

Legionnaires' Disease – Although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Contraindication: Known hypersensitivity to this antibiotic.

Warnings: (See Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy – Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Recent studies of erythromycin reveal that its use in patients receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In such a case, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, overgrowth of nonsusceptible bacteria or fungi is possible. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported. [013079]

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration.

See adjoining column for summary of prescribing information.

Subacute Thyroiditis in a 4½-Year-Old Girl

Subacute thyroiditis is distinguished from "acute thyroiditis" by virtue of cause rather than mode of onset. Acute thyroiditis is bacterial in origin, usually with abscess formation. Subacute thyroiditis is generally thought to be viral. In 1973, Kirkland et al[1] reported a total of 36 cases of acute thyroiditis in children.[2] However, subacute thyroiditis is mentioned in only two pediatric case reports.[2,3] Studies in the adult literature mention five other cases of subacute thyroiditis.[4-8] We report an additional case in a 4½-year-old girl.

Report of a Case.—A 4½-year-old girl experienced fever and otitis media of the left ear six days prior to admission. Ampicillin sodium (250 mg) four times a day and a decongestant were given. The fever persisted, and she complained of dysphagia. Penicillin G benzathine (Bicillin), 600,000 units, was given. Two days later, anterior neck pain and thyroid swelling occurred.

Physical examination revealed a child in extreme discomfort, who kept her neck in a flexed position. Positive physical findings were limited to the head and neck region. Both tympanic membranes were retracted and dull. Her thyroid gland was exquisitely tender and diffusely enlarged to about three times normal size.

The WBC count was 15,700/cu mm, with 73% polymorphonuclear cells, 5% band forms, and 22% lymphocytes. The ESR was 58 mm/hr; urinalysis showed proteinuria (1+) and 3+ ketones, five to ten WBCs per high-power field (HPF), and ten to 20 RBCs per HPF on a centrifuged specimen. A repeated urinalysis 48 hours later showed normal findings.

The spinal fluid had no cells, a protein level of 11 mg/dL, and a glucose level of 83 mg/dL. A slide test for heterophil antibody of infectious mononucleosis was negative. The serum protein-bound iodine level was 11.3 mg/mL; serum thyroxine (T_4), (by radioimmunoassay) .12.1 mg/dL; triiodothyronine (T_3) uptake, 34%; serum thyroid-stimulating hormone (TSH), less than 1.5 μU/mL; and serum T_3, 118 ng/dL. Blood, urine, and throat cultures were negative. The serum amylase value was 5 IU/L (normal). Findings on ultrasound examination of the thyroid were consistent with diffuse enlargement secondary to edema. A test for antiepithelial thyroid antibodies was negative. Thyroid uptake (iodine 123) was 3.6% at six hours and less than 1.0% at 24 hours. This is consistent with thyroiditis. Normal values are 18% at six hours and 18% to 35% at 24 hours.

The patient continued to have daily spiking temperatures to 39.5 °C. Ampicillin therapy was continued, and after 48 hours, oxacillin (200 mg/kg daily) was added. There was no improvement after another 72 hours.

An endocrinology consultant believed that this child had subacute thyroiditis. Therefore, prednisone therapy (2 mg/kg/day) was started. She had one more temperature spike to 39.5 °C and then rapid defervescence. Her thyroid gland rapidly diminished in size and tenderness during the next 48 hours. She was discharged seven days after admission. Unfortunately, no viral cultures were taken.

Prednisone dosage was slowly decreased during an additional ten days. A T_3 uptake value was 27%; serum T_4, 6.9 mg/dL; and serum TSH, 8.2 μU/mL. Her gland returned to normal size and she has been asymptomatic for more than one year.

Comment.—As illustrated by this case, it is difficult to know whether one is dealing with an acute or subacute process when presented with a child with an acutely enlarged, tender thyroid gland.

Differential Diagnosis

	Acute (Suppurative) Thyroiditis	Subacute (Nonsuppurative) Thyroiditis
Age range	Rare in all age groups, but most common in children and young adults	Adults; extremely rare in children
Sex ratio	M = F	60%-100% F
Mode of onset	Acute	Often acute, but may be insidious
Fever	Present	Present
Thyroid swelling	Usually unilateral, often with fluctuant area	Usually diffuse, but may be unilateral or migrate between lobes
WBC count	Usually elevated with a left shift on differential cell count	Usually normal, but may be elevated to 20,000/cu mm; usually normal differential cell count
ESR	Elevated	Markedly elevated, often 100 mm/hr
Blood cultures	May be positive	Negative
Abscess	Present	Absent
Serum triiodothyronine and thyroxine levels	Normal	Usually normal; may see hyperthyroidism followed by a hypothyroid phase and a recovery period
Radioactive iodine uptake	No data	Decreased
Treatment	Antibiotics and drainage	Thyroid replacement and salicylates, steroids for severe cases

Differential diagnosis is important since the therapy is markedly different. Acute suppurative thyroiditis is often preceded by an upper respiratory tract infection or otitis media. Usual symptoms include fever, sore throat, dysphagia, and painful thyroid swelling. Usually, one lobe of the thyroid gland is enlarged, with warmth and erythema. This lobe later becomes fluctuant. There is usually leukocytosis with a left shift on the differential cell count and an elevated ESR. The patients are euthyroid. Ultrasonography can be helpful in identifying an abscess. The most common organisms are streptococci, staphylococci, and pneumococci,[9] although anaerobic bacteria have been reported recently.[10] Treatment consists of drainage of the abscess, cultures of the purulent material, and appropriate antibiotic therapy.

Subacute thyroiditis in adults was reviewed extensively by Greene in 1971.[11] Thyroid pain and swelling are the most consistent symptoms; the onset may be acute or insidious. Sore throat, fatigue, weakness, malaise, weight loss, and low-grade fever are often reported. Usually there is diffuse bilateral swelling. Swelling can also migrate from one lobe to another. The WBC count and differential cell count are usually normal. The ESR is always elevated, often higher than 100 mm/hr in the first month of illness. Normochromic anemia and decreased serum albumin and elevated globulin levels have been noted.[11] Thyroid function test results are usually normal, although the patient may become acutely hyperthyroid, presumably through release of preformed thyroid hormone from the damaged gland. This may be followed by a hypothyroid phase and then recover to normal function.[12,13]

Viral infections most often associated with subacute thyroiditis are mumps, measles, influenza, infectious mononucleosis, coxsackie virus, and adenovirus.[11] Treatment consists of thyroid replacement and salicylates for mild cases, with corticosteroid therapy reserved for the severely ill. The Table gives the pertinent distinguishing characteristics of these two diseases.

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1. Kirkland RT, Kirkland JL, Rosenberg HS, et al: Solitary thyroid nodules in 30 children and report of a child with a thyroid abscess. *Pediatrics* 51:85-89, 1973.
2. Hung W: Mumps thyroiditis and hypothyroidism. *J Pediatr* 74:611-613, 1969.
3. Radfar N, Kennery F, Larsen PR: Subacute thyroiditis in a lateral ectopic thyroic gland: Evaluation of the pituitary-thyroid axis during the acute destructive and recovery phases. *J Pediatr* 87:34-37, 1975.
4. St John J, Nicholson W: An evaluation of the treatment of thyroiditis. *South Med J* 44:1059-1062, 1951.
5. Jackson AS, Gilman LC: Thyroiditis. *Am J Surg* 88:891-895, 1954.
6. Hamberg BA, Hintze G, Lussile R, et al: Subacute thyroiditis. *Acta Endocrinol* 33:457-472, 1960.
7. Hamburger JI: Subacute thyroiditis: Diagnostic difficulties and simple treatment. *Nucl Med* 15:81-89, 1974.
8. Chamberlain JL: Acute thyroiditis: Report of a case in a child. *Ky Med Assoc* 65:1001-1002, 1966.
9. Hazard JB: Thyroiditis: A review. *Am J Clin Pathol* 15:289, 298, 1955.
10. Abe K, Taguchi T, Okuno A, et al: Recurrent acute suppurative thyroiditis. *Am J Dis Child* 132:990-991, 1978.
11. Greene J: Subacute thyroiditis. *Am J Med* 51:97-108, 1971.
12. Basterie PA, Ermans AM: *Thyroiditis and Thyroid Function*. New York, Pergamon Press, 1972, pp 69-97.
13. Larsen PR: Serum triiodothyronine, thyroxine, and thyrotropin during hyperthyroid, hypothyroid and recovery phases of subacute nonsuppurative thyroiditis. *Metabolism* 23:467-471, 1974.

Liver Herniation Presenting as Respiratory Distress and Cardiomegaly

Respiratory distress and cardiomegaly in the immediate postnatal period are most frequently due to primary disease of the lungs or the vascular system. Herniation of the liver through the diaphragm into the chest cavity is rare, but can cause respiratory embarrassment and cyanosis.[1] Hypoplastic left heart syndrome, coarctation of the aorta, and Ebstein's anomaly of the tricuspid valve all may manifest cardiomegaly and respiratory distress.[2] Sepsis,[3] hypocalcemia,[4] and asphyxia[5] have also produced such findings. The following case report is one of congenital liver herniation manifesting respiratory distress and generalized cardiomegaly. Previously reported cases of liver herniation have not mentioned cardiomegaly as an early finding.

Report of a Case.—A 6-hour-old boy was admitted because of progressive tachypnea and cyanosis beginning one hour after birth. Vaginal delivery was uneventful, with Apgar scores of 8 and 9 at one and five minutes, respectively. Birth weight was 3,843.8 g. The 30-year-old mother is gravida 3, para 1, and in good health.

On physical examination, respirations were 90/min, heart rate 180 beats per minute, and rectal temperature was 37.3 °C. Blood pressure was 81/36 mm Hg in the right arm and 80/40 mm Hg in the right leg.

Laboratory tests revealed a normal hemoglobin level, WBC count, and differential count. An arterial blood sample while the baby was receiving 50% inspired oxygen showed a pH of 7.33, a P_{CO_2} of 32 mm Hg, and a P_{O_2} of 117 mm Hg. Serum electrolyte, calcium, and glucose levels were normal.

The chest roentgenogram was interpreted as showing massive cardiomegaly (Fig 1 and 2) and possible elevation of the right hemidiaphragm. An echocardiogram excluded pericardial effusion and was negative for intramyocardial masses. The ECG was normal for age.

Right-sided heart catheterization demonstrated elevated right ventricular and pulmonary artery pressures (50/0-6 mm Hg and 50/30 mm Hg, respectively). Angiography showed that the heart and left lung were displaced into the left thoracic cavity by a nonvascular mass. The venous return, arterial system and size, and configuration of the heart's chambers were normal.

The chest was opened with a midline sternotomy to reveal a distended pericardial sac containing 15 mL of fluid. At opening of the pericardium, a 4 × 6-cm saccular mass was found. The mass displaced the heart and indented the lateral wall of the right ventricle. The sac then was opened and revealed liver tissue. After returning the liver to the abdomen, the eventrated portion of the diaphragm was

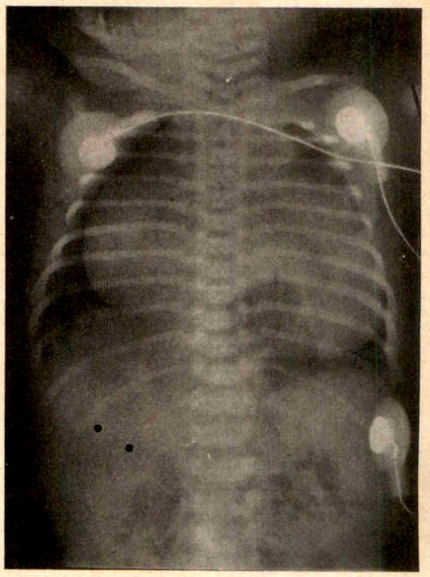

Fig 1.—Chest roentgenogram showing generalized cardiomegaly.

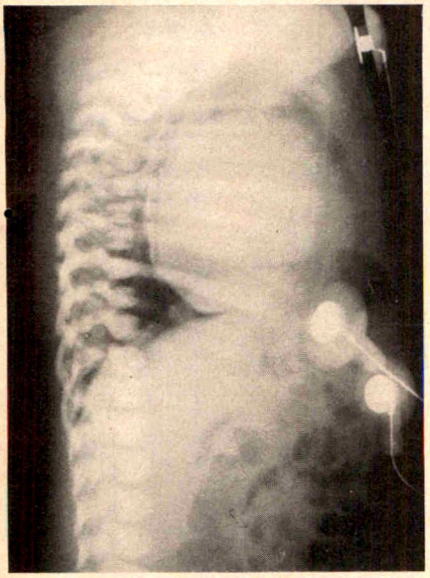

Fig 2.—Chest roentgenogram, lateral view, showing generalized cardiomegaly.

repaired with direct sutures that extended to the chest wall anteriorly. The postoperative course was uneventful. A postoperative roentgenogram revealed a normal cardiac silhouette.

Comment.—Developmentally and anatomically, the diaphragm is an organ with several potential points for herniation, the most frequent sites being the foramen of Bochdalek, the esophageal hiatus, and the foramen of Morgagni.[6] Diaphragmatic herniation on the left is 12 times as common as on the right, with the bowel being the most common organ found in the chest cavity.[7] Liver herniation is extremely rare. A review of 83 hernias through the foramen of Morgagni revealed one case of combined liver and colon herniation; no cases had only liver in the sac.[8]

Respiratory difficulties and increase in the size of the heart in the immediate postnatal period are most commonly ascribed to congenital heart disease such as hypoplastic left heart syndrome, Ebstein's anomaly of the tricuspid valve, coarctation of the aorta, and truncus arteriosus. Infants of diabetic mothers and severely hypoglycemic neonates may have combined cardiorespiratory symptoms. Sepsis and hypoglycemia have also been reported to cause such findings.

This case demonstrates that although herniation of the liver through the right diaphragm is infrequent, it should be considered in the infant with respiratory distress and cardiomegaly. Aids to diagnosis prior to surgery may include chest roentgenography,[9] liver scan,[10] pneumoperitoneum,[11,12] echocardiogram, and cardiac catheterization. Therapy prior to surgery should be directed toward the relief of symptoms; the asymptomatic infant may require no invasive procedures.

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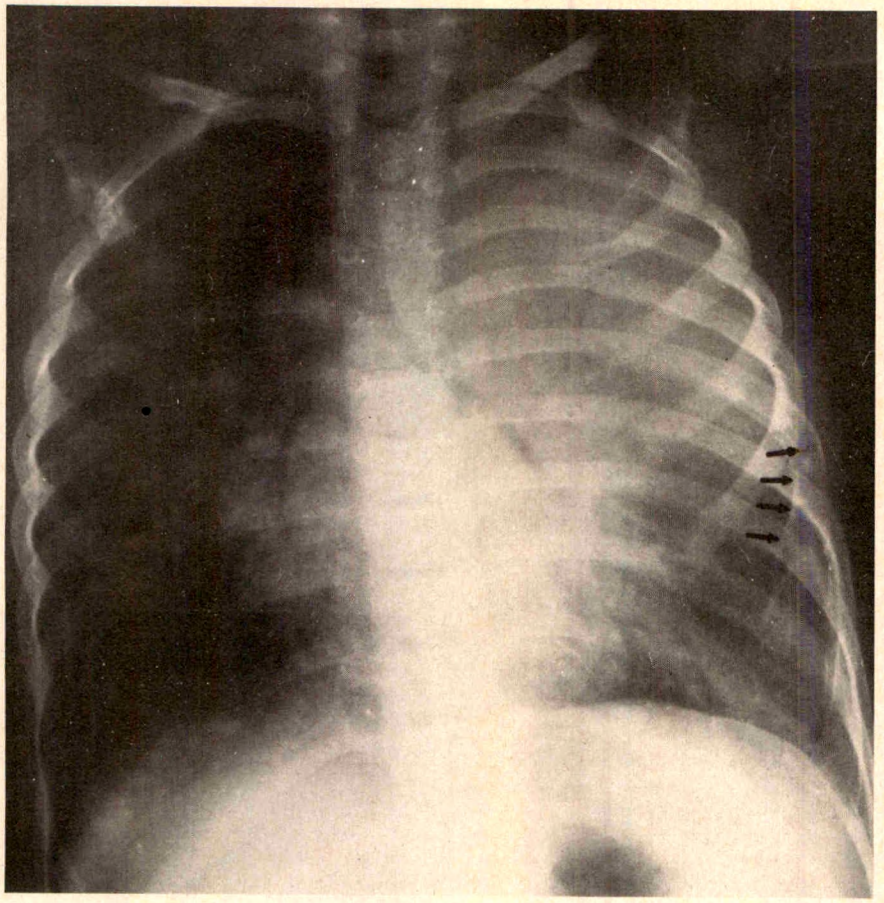
1. Ravitch MM, Handelsman JC: Defects in right diaphragm of infants and children with herniation of liver. *Arch Surgery* 64:794-802, 1952.
2. Moss AJ, Adams F: *Heart Disease in Infants, Children, and Adolescents.* Baltimore, Williams & Wilkins Co, 1977, p 262.
3. Postel J, Schloerb PR: Cardiac depression in bacteremia. *Ann Surg* 186:74-82, 1977.
4. Roberton NR, Smith MA: Early neonatal hypocalcemia. *Arch Dis Child* 50:604-609, 1975.
5. Rowe RD, Hoffman T: Transient myocardial ischemia of the newborn infant: A form of severe cardiorespiratory distress in full term infants. *J Pediatr* 79:243-250, 1972.
6. Bradley JE, Greiner DJ: Diaphragmatic hernia. *Am J Dis Child* 66:143-148, 1943.
7. Kaufman SA, Madoff IM: Intrathoracic accessory lobe of liver. *Ann Intern Med* 53:403-407, 1960.
8. Craighead C, Strug L: Diaphragmatic deficiency in retrocostoxiphoid area. *Surgery* 44:1062-1069, 1958.
9. Campbell J: The diaphragm in roentgenology of the chest. *Rad Clin North Am* 1:395-410, 1963.
10. Armstrong RG, Stanford W: Liver scan in the diagnosis of liver hernia. *Acad Fam Pract Gen Pract* 1:87-89, 1970.
11. Berger RL, Rodriquez-Aquero J, Madoff IM: Herniation of the liver through the foramen of Morgagni. *N Engl J Med* 276:243-245, 1962.
12. Vaughn CC: Diagnosis of localized eventration. *Dis Chest* 54:467-469, 1968.

Aspergillosis in Chronic Granulomatous Disease: Therapeutic Considerations

Children with chronic granulomatous disease (CGD) are susceptible to a wide variety of catalase-positive microorganisms.[1] *Aspergillus* infections are particularly difficult to diagnose and treat. Aspergilli may invade many tissues, including the lung,[1,2] thyroid,[3] and bone,[4] and diagnosis frequently requires culture of surgical specimens. Therapy for aspergillosis in children with CGD by use of amphotericin B alone is frequently suboptimal, and several patients have required granulocyte transfusions in addition to amphotericin B.[1,2] The need for potentially synergistic combinations of antimicrobials is particularly keen in children with CGD. We report a case of aspergillosis involving the ribs, lung, and pleura that was successfully treated with the combination of amphotericin B and rifampin.

Method of Susceptibility Testing.—The clinical isolate of *A fumigatus* was grown on Sabouraud's ager slants for seven days. The method of harvesting and quantitating the inocula of the aspergillus and the control organism *Candida albicans* as well as the preparation of amphotericin B and flucytosine is described elsewhere.[5] Rifampin was similarly prepared except that it was initially dissolved in methyl alcohol. Susceptibility testing was performed using a tube dilution method described by Shadomy and Espinel-Imgrao.[6] Synergy was tested for using standard checkerboard techniques. In both drugs, a fourfold decrease in the concentrations necessary to produce inhibitory or lethal activity was considered synergistic. Any decrease in concentrations less than fourfold was considered additive.

Report of a Case.—A 27-month-old male infant known to have CGD was readmitted to State University of New York Hospital, Brooklyn, with a history of fever and a fluctuant mass over the left lateral chest wall. X-linked CGD was diagnosed at 6 months of age when a *Serratia marcescens* osteomyelitis of his calcaneus developed. He was successfully treated, and therapy was begun with sulfamethoxazole and trimethoprim for the 18 months prior to his readmission. The diagnosis of CGD was based on a negative qualitative nitroblue tetrazolium test (NBT) with and without endotoxin stimulation, a markedly reduced quantitative NBT test, and an abnormal microbial killing assay. On physical examination, he appeared to be acutely ill with a temperature of 38.3 °C. Two tender masses were noted over the lateral aspect of his left hemithorax. Chest films revealed extensive left-sided pulmonary infiltration and pleural reaction (Figure). Lytic lesions and periosteal reaction were also noted in the left fourth, fifth, sixth, and seventh ribs. A gallium citrate Ga 67 scan confirmed the presence of inflammation in these ribs. Serology performed to a variety of fungi revealed a complement fixation (CF) titer of 1:64 for *Aspergillus*. One of the masses overlying the chest was explored, and pus containing septate



Lytic lesions and periosteal reaction noted in left fourth, fifth, sixth, and seventh ribs (arrows).

hyphae on stain with lactophenol cotton blue was obtained. *Aspergillus fumigatus* grew in pure culture from the purulent material obtained from these masses as well as from a biopsy specimen of the rib and bone marrow aspirate. Susceptibility testing of the *Aspergillus* to flucytosine, amphotericin B, and rifampin, as well as synergy studies, were performed (Table). The child was begun on therapy with amphotericin B, 0.2 mg/kg/day, and the dosage was gradually increased to 1 mg/kg/day. He was also given rifampin, 10 mg/kg/day orally in two doses. He received alternate-day therapy with amphotericin B after a serum level of 1.95 μg/mL had been achieved. Gradual healing of the lytic areas in his ribs occurred, and he was maintained on a regimen of alternate-day amphotericin B for two months. He was discharged from the hospital on a rifampin regimen and was given amphotericin B twice weekly as an outpatient. His total dose of amphotericin B was 380 mg at the time of its discontinuation four months after admission. Repeated serology studies performed six weeks after therapy was begun showed a CF reaction to *Aspergillus* of 1:16 and a titer of 1:4 four months after admission. The child appears well, without recurrence of his aspergillosis nine months since his discharge from the hospital.

Comment.—Children with chronic granulomatous disease have an immunologic defect inherent in their phagocytes. In most families, this defect is inherited through an x-linked gene.[7] Although neutrophils from these children migrate and phagocytize bacteria and fungi, they are unable to kill those that are catalase positive, thereby leading to the intracellular persistence of these organisms. Once an infection has occurred, specific therapy should be instituted, where feasible, with bactericidal activity that penetrates phagocytes well. When these therapeutic criteria cannot be met or therapy appears unsuccessful, granulocyte transfusions may be necessary.[1,2,8] Our patient had osteomyelitis with an *Aspergillus* whose minimum inhibitory concentration (MIC) was within easily achievable serum levels of amphotericin B and whose minimum lethal concentration was at maximally achievable serum concentrations (Table). The combination of amphotericin B and rifampin has been shown to be synergistic for some aspergilli in vitro[9] and in animal models.[10] Kitahara et al[9] found this combination to be synergistic in vitro against six of six clinical isolates of aspergilli as evidenced by a marked decrease in MICs, the incorporation of tritium uridine into RNA, and growth weights of the aspergilli when compared with those obtained by amphotericin B alone. Similarly, Arroyo et al[10] found the addition of rifampin to amphotericin B superior to amphotericin B alone in the therapy of disseminated aspergillosis in mice as judged by a significantly higher survival rate in those mice receiving combined therapy. Depending on the inoculum size and dose of rifampin added to amphotericin B, 40% to 100% of mice survived on combined therapy, 10% to 30% on amphotericin B alone, and 0% to 10% of controls after one month of observation. These studies suggest that combination chemotherapy may prove to be of benefit in aspergillosis as it has in other fungal infections.[11] As can be seen in the Table, rifampin also synergistically potentiated the lethal activity of amphotericin B for our isolate in vitro and we believed that it might decrease either the dose or duration of amphotericin B therapy required for successful treatment. The "static" and lethal activity of amphotericin B was also increased in vitro by flucytosine. The degree of potentiation was not as marked, however, as that observed with rifampin. It should be noted that when the concentration

Antimicrobial Therapy Against *Aspergillus fumigatus**

	MIC	MLC
Rifampin	>64	>64
Flucytosine	>250	>250
Amphotericin B	0.98	1.95
Rifampin/amphotericin B	0.08/0.5	1.25/0.5
Flucytosine/amphotericin B	0.12/0.5	62.5/0.5

*Minimum inhibitory concentration (MIC) and minimum lethal concentration (MLC), measured in micrograms per milliliter, of rifampin, flucytosine, and amphotericin B alone and in combination.

of amphotericin B was decreased to 0.25 μg/mL, neither lethal nor inhibitory activity could be demonstrated against our isolate no matter what concentrations of flucytosine or rifampin were added. The resolution of the lytic rib lesions and the patient's thoracic granulomata and the decrease in his CF titers suggest that the combined use of rifampin and amphotericin B should be considered in a child with CGD and aspergillosis.

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1. Bujak JS, Kwon-Chung KJ, Chusid MJ: Osteomyelitis and pneumonia in a boy with chronic granulomatous disease of childhood caused by a mutant strain of *Aspergillus nidulans*. *Am J Clin Pathol* 61:361-367, 1974.

2. Raubitschek AA, Levin AS, Stites DP, et al: Normal granulocyte infusion therapy for aspergillosis in chronic granulomatous disease. *Pediatrics* 51:230-233, 1973.

3. Halazun JF, Anast CS, Luken JN: Thyrotoxicosis associated with aspergillus thyroiditis in chronic granulomatous disease. *J Pediatr* 80:106-108, 1972.

4. Simpson MB, Merz WG, Kurlinski JP, et al: Opportunistic mycotic osteomyelitis: Bone infections due to *Aspergillus* and *Candida* species. *Medicine* 56:475-482, 1977.

5. Corrado ML, Weitzman I, Stanek A, et al: Subcutaneous infection with *Phialophora richardsiae* and its susceptibility to 5-fluorocytosine, amphotericin B, and miconazole. *Sabouraudia* 18:97-104, 1980.

6. Shadomy S, Espinel-Imgrafo A: Susceptibility testing of antifungal agents, in Lennette EH, Spaulding EH, Truant JP (eds): *Manual of Clinical Microbiology*, ed 2. Washington, DC, American Society for Microbiology, 1974, pp 571-573.

7. Maish WL: *Chronic Granulomatous Disease: The McLeod Syndrome, and the Kell Blood Group*. Birth defects original article series, New York, National Foundation March of Dimes, 1978, vol 14, no 6a, pp 9-25.

8. Cohen MS, Isturig RE, Malech HL, et al: Fungal infections in chronic granulomatous disease (CGD) (abstract No. 670). Read before the 19th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, Oct 4, 1979.

9. Kitahara M, Seth VK, Medoff G, et al: Activity of amphotericin B, 5-fluorocytosine, and rifampin against six clinical isolates of *Aspergillus*. *Antimicrob Agents Chemother* 9:915-919, 1976.

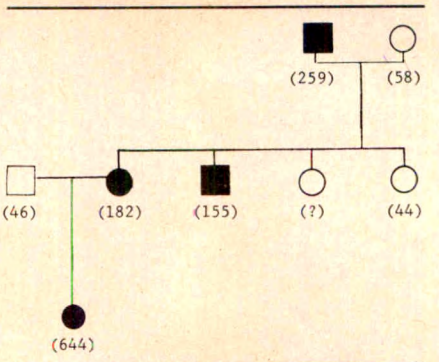
10. Arroyo J, Medoff G, Kobayashi GS: Therapy of murine aspergillosis with amphotericin B in combination with rifampin or 5-FC. *Antimicrob Agents Chemother* 11:21-25, 1977.

11. Bennett JE, Dismukes WE, Duma RJ, et al: A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* 301:126-131, 1979.

Asymptomatic Familial Elevation of Serum Alkaline Phosphatase Levels

Asymptomatic elevation of serum alkaline phosphatase levels has been reported recently in one family. An autosomal dominant inheritance was suggested by father-son transmission.[1] Both liver and bone isoenzyme levels were elevated. We describe another family that had elevations of serum alkaline phosphatase levels without apparent disease. In this family, the heat labile fraction (representing the bone isoenzyme level) was greater than 90% in all affected individuals.

Report of a Case.—An 11-year-old asymptomatic girl was found to have an elevated serum alkaline phoshatase level after the incidental discovery of an increased level in her mother. Extensive investigations failed to reveal a cause for the elevated level in the mother. Results of a physical examination of the daughter were entirely normal. Results of laboratory studies, including complete blood cell count, urinalysis, and serum chemistries, were normal except for a fasting serum alkaline phosphatase level of 664 IU/L (normal, 40 to 110 IU/L). Other laboratory values were as follows: SGPT, 11 IU/L (normal, ≤ 40 IU/L); serum γ-glutamyl transpeptidase, 13 IU/L (normal, 2 to 40 IU/L); serum 5′nucleotidase, 8 Bodansky units/mL (normal, 2 to 17 BU/mL); albumin-globulin ratio, 1.7; serum ceruloplasmin, 38 mg/dL (normal, 20 to 50 mg/dL); serum α_1-antitrypsin, 170 mg/dL (normal, 150 to 275 mg/dL); serum calcium, 9.2 mg/dL; and serum phosphorus, 3.8 mg/dL. Subsequent evaluations revealed persistently elevated serum alkaline phosphatase levels, negative hepatitis B surface antigen, and negative urinary viral isolation studies. Roentgenographic examinations revealed a normal oral cholecystogram and skeletal survey. An isotopic bone scan was normal. Serum alkaline phosphatase activity determined by the International Method was 96% heat labile. Evaluation of the mother's enzyme activity revealed 92% to be heat labile. The enzyme activity of a maternal uncle and grandfather was also predominantly heat labile (94%) (Fig 1). A dietary history showed no deficiency.



Family pedigree, with top being maternal grandparents, middle, parents and maternal uncle and aunts, and bottom, patient of our study. Solid symbols indicate members with elevated serum alkaline phosphatase activity; open symbols, members with normal activity; squares, males; circles, females. Numbers in parentheses represent serum alkaline phosphatase values, IU/L (normal, 40 to 110 IU/L).

Comment.—An elevated serum alkaline phosphatase level unrelated to physiological conditions such as skeletal growth or pregnancy is often regarded as evidence of a pathologic condition.[2] Pathologic elevations of serum alkaline phosphatase levels are most often associated with disorders of the liver and bone; however, a wide variety of diverse diseases may occasionally cause an elevation in the enzyme level. Disorders causing an elevation of the heat labile fraction of the enzyme are as follows: physiologic growth, fractures, primary and secondary hyperparathyroidism, osteomalacia, rickets, Paget's disease, primary or metastatic neoplasms, acromegaly, polyostotic fibrous dysplasia, osteogenesis imperfecta, familial osteoectasia, hereditary osteolysis, and primary hypophosphatemia.[2-5,7]

As there are usually many other signs, symptoms, or laboratory abnormalities indicating disorders of liver or bone, there is often no need to identify the specific isoenzymes.[3] However, when an elevation of the serum alkaline phosphatase level is found in an otherwise healthy person, an identification of the source of the enzyme is desirable.[3] This determination may be accomplished directly by heat or urea stability tests, electrophoretic separation, or amino acid inhibition testing, or indirectly by determination of other hepatobiliary enzymes such as 5′nucleotidase, leucine aminopeptidase, and γ-glutamyl transpeptidase.[5,6]

An asymptomatic family was recently described in which elevations in

serum alkaline phosphatase levels seemed to be inherited in an autosomal dominant manner.[1] There was increased activity of both bone and liver isoenzymes. In the family we examined, elevations of the enzyme levels in the absence of disease seemed to be transmitted in an autosomal dominant manner as well. However, the presence of a predominantly heat labile fraction would suggest a different abnormality in enzyme homeostasis in the two families. The evaluation of elevated serum alkaline phosphatase levels should include enzyme determinations in family members if other diagnostic studies are inconclusive.

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1. Wilson JW: Inherited elevation of alkaline phosphatase activity in the absence of disease. *N Engl J Med* 301:983-984, 1979.
2. Wolf PL: Clinical significance of an increased or decreased serum alkaline phosphatase level. *Arch Pathol Lab Med* 102:497-501, 1978.
3. Kaplan MK: Alkaline phosphatase. *Gastroenterology* 62:452-468, 1972.
4. Stolbach LL: Ectopic production on an alkaline phosphatase isoenzyme in patients with cancer. *N Engl J Med* 281:757-762, 1969.
5. Cleeve HJW: Origin of an elevated plasma alkaline phosphatase activity in non-jaundiced patients. *Ann Clin Biochem* 15:86-90, 1978.
6. Davidson FD: Use of the albumin/globulin ratio in differentiation between bone and liver isoenzymes of alkaline phosphatase. *Clin Chem* 24:2214-2215, 1978.
7. Hamilton DV, Potasman I: Thyroid disease and alkaline phosphatase. *Ann Intern Med* 90:440-441, 1979.

Argininosuccinicaciduria: The Hair Abnormality Revisited

Argininosuccinicaciduria is a rare genetic error of the Krebs-Henseleit urea cycle due to the absence or deficiency of the enzyme argininosuccinate lyase and is associated with mental retardation, seizures, ataxia, and hepatomegaly. Hyperammonemia may or may not be present, but blood urea levels are always within normal limits. Abnormally fragile hair has been detected in about half of the reported cases, and in some, a morphologic hair alteration termed trichorrhexis nodosa has been observed.[1] The nature of the hair defect has not been extensively studied, and tensile strength and other physical properties have been measured in only a single case, to our knowledge.[2] Amino acid analysis of acid hydrolysates of our patient's hair revealed a reduction in cystine content to 50% of the control level, concomitant with a similar degree of reduction of values for tensile strength and Young's modulus. No relationship between the urea cycle block, the amino acid alteration in hair protein, and the phenotypic expression of the disorder, particularly the mental retardation, could be established or discerned.

We have continued to study this patient for seven years. The urinary excretion of argininosuccinic acid continues unabated at the same order of magnitude as during the period of the initial diagnoses (2.5 mM/g creatinine), and the child remains severely mentally retarded. However, a distinct improvement in hair appearance has occurred together with a substantial increase in hair cystine content to about 75% of the normal level. Measurement of tensile strength and Young's modulus at this time similarly revealed a notable change in the direction of normal values.

Comment.—Amino acid analysis and measurement and calculation of physical attributes were carried out as previously described.[2] Assessment of intellectual function was made by neurological examination and by reports of special education instructors.

Figure 1 summarizes the results of cystine measurements, tensile strength, and Young's modulus values as a function of age and as a percentage of the normal value. Control measurements were made using hair obtained from six age-matched, nonhospitalized neighborhood children apparently in good health. A gradual increase in cystine content and tensile strength occurred between 5 and 10 years of age, with a marked additional improvement over the next two years. The figure also shows that a much earlier and more pronounced increase in values for Young's modulus occurred. Thus, correction of the defect in the elastic properties of the hair preceded and exceeded the correction in overall tensile strength and total cystine content.

Figure 2 compares the appearance of the hair at diagnosis and seven years later. The mother reports that the child's pillow is not now covered with short, broken-off fragments of hair as it had been during the initial period of study. Early speculations concerning the abnormality were related to a possible arginine deficiency in the hair.[1] An improvement in quality and/or quantity of the hair was reported to have occurred after supplementation of the diet with arginine[3] or with a high protein content.[4] However, arginine levels were not measured either before or after treatment in these cases. In our patient, arginine levels in the hair were dis-

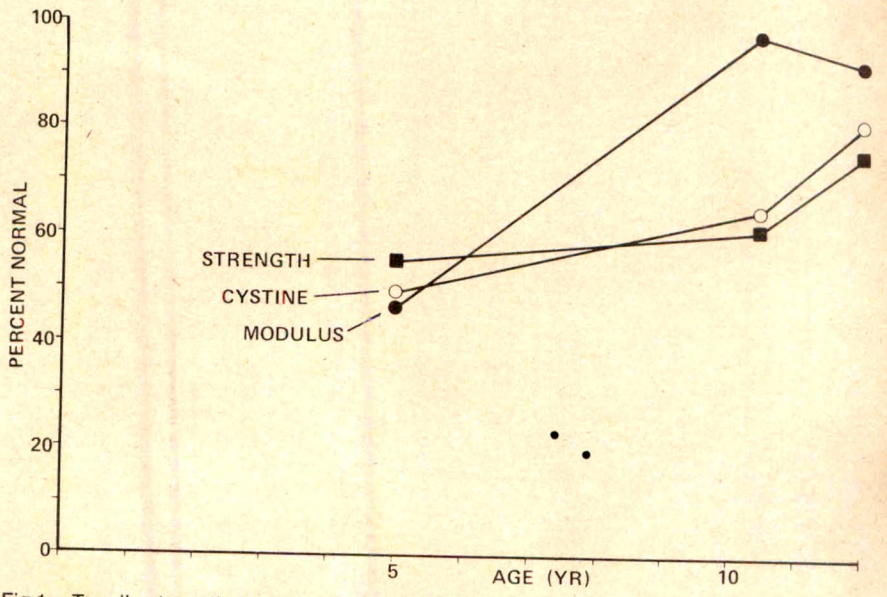

Fig 1.—Tensile strength, Young's modulus, and cystine content as function of age in hair of patient.

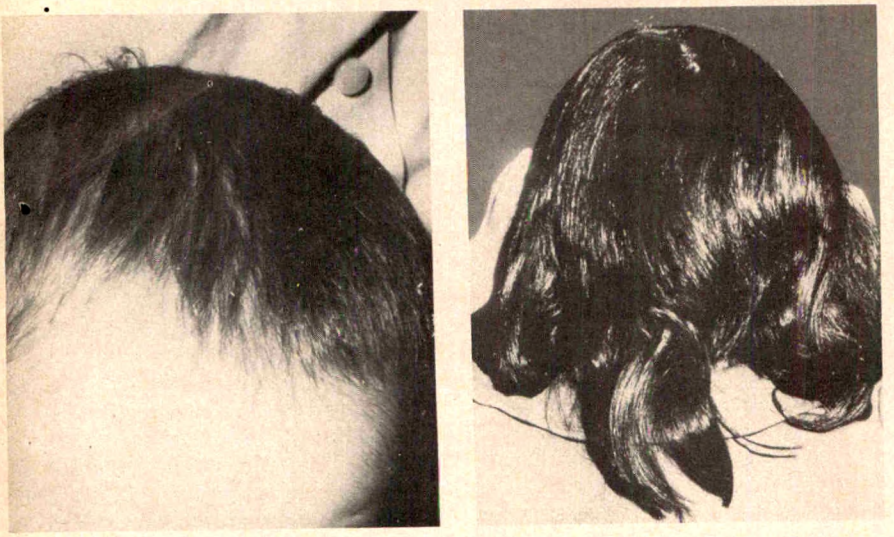

Fig 2.—Appearance of patient's hair at diagnosis (left) and seven years later (right).

tinctly within the normal range. Baden and Shih[5] have described two patients with normal amino acid levels in the hair, but it was not stated whether the hair was brittle in these patients. It is of interest that the sulfur-containing amino acids play a major role in the altered chemical and physical properties of hair in both acquired and genetic disorders.[6,7] The water content of the patient's hair, determined by the method of Gold and Scriver,[6] was not notably different from the normal control hair.

R. J. Pollitt has reported (written communication, July 17, 1974) that the brittle hair of one of the first patients discovered with this disorder now appears to be completely normal 20 years later, but no chemical or physical measurements were mentioned. Not enough information is available at this time to even speculate whether the hair defect is genetic and related to the urea cycle block, genetic and unrelated, acquired, or some combination of these factors. Similarly, the cystine deficiency cannot reasonably be related to the primary enzymic deletion. However, a clinical appraisal of the quality, quantity, and distribution of body hair should remain an important facet of the physical examination of any patient. The initial indication for an amino acid workup in our patient was based on the observation by an astute house officer who commented on the shortness of the patient's hair, though it had not been recently cut. The structure of keratin in normal and abnormal states represents a complex problem in the chemistry and physical chemistry of an abundant and easily obtainable protein. Its alteration in genetic and acquired diseases and susceptibility to hormonal influences are important facets of biologic mechanisms, and its study may reveal clues related to the basic mechanisms of underlying diseases.[8]

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1. Shih VE: Urea cycle disorders and other congenital hyperammonemic syndromes, in Stanbury JB, Wyngaarden JB, Fredrickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 4. New York, McGraw-Hill Book Co, 1978, pp 362-386.

2. Potter JL, Timmons GD, West R, et al: Arginosuccinicaciduria: The hair abnormality. *Am J Dis Child* 127:724-727, 1974.

3. Hartlage PL, Coryell ME, Hall WK, et al: Argininosuccinic aciduria: Perinatal diagnosis and early dietary management. *J Pediatr* 85:86-88, 1974.

4. Coryell ME, Hall WK, Thevaos TG, et al: A familial study of a human enzyme defect, argininosuccinic aciduria. *Biochem Biophys Res Commun* 14:307-312, 1964.

5. Baden HP, Shih VE, cited by Shih VE: Urea cycle disorders and other congenital hyperammonemic syndromes, in Stanbury JB, Wyngaarden JB, Fredrickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 4. New York, McGraw-Hill Book Co, 1978, pp 362-386.

6. Gold RJM, Scriver CR: The characterization of hereditary abnormalities of keratin: Clouston's ectodermal dysplasia, in Bergsma D (ed): *Third Conference on the Clinical Delineation of Birth Defects: Part XII*. Baltimore, Williams & Wilkins Co, 1971, pp 91-95.

7. Brown AG: Congenital hair defects, in Bergsma D (ed): *Third Conference on the Clinical Delineation of Birth Defects: Part XII*. Baltimore, Williams & Wilkins Co, 1971, pp 52-68.

8. Porter PS: The genetics of human hair growth, in Bergsma D (ed): *Third Conference on the Clinical Delineation of Birth Defects: Part XII*. Baltimore, Williams & Wilkins Co, 1971, pp 69-85.

CORRECTION

Phrase Omitted.—In the article entitled "Hypernatremic Dehydration of Infancy," published in the August JOURNAL (134:785-792, 1980), a phrase was inadvertently omitted. On page 789, in the second column, second paragraph, the third sentence should have read as follows: "Two studies in Great Britain have shown that a random urine osmolality is likely to be higher in a healthy formula-fed infant than in a healthy breast-fed infant."

Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

Bartter's Syndrome

Sir.—I read with interest in the JOURNAL (133:636-638, 1979) the article by Robson, Arbus, and Balfe, "Bartter's Syndrome: Differentiation Into Two Clinical Groups"; it confirms the findings I published with David et al in 1976.[1] In addition, I observed that the infusion of angiotensin II produced an increase in urinary sodium excretion only in the patients with sodium wasting and that this renal sodium wastage occurred despite an increased aldosterone secretion.

I could not confirm some points made by the authors about the difference between the two groups. There was no difference in age between the two groups; the two patients with salt wastage were seen after the age of 3 years (5½ and 13 years), and the youngest of our patients (3½ years) showed no sodium wastage. Our findings were similar to those of Wald et al.[2] Hypomagnesemia was observed only in our patient with sodium wastage.

The reason or reasons why some patients exhibit sodium wastage and others do not is not, to my knowledge, known. According to our preliminary results, infusion of saralasin acetate (an inhibitor of angiotensin II that lowers the secretion of aldosterone) produced an increase in urinary sodium excretion in a patient without sodium wastage, whereas no change of urinary sodium excretion was observed in a patient with sodium wastage. These results suggest that the patients with sodium wastage would exhibit an escape from aldosterone activity that is not observed in the patients without renal sodium wastage. The existence or absence of sodium wastage in Bartter's syndrome raises also the problem of whether the etiology is similar in the two groups.[2,3]

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Nonproprietary Name and Trademark of Drug

Saralasin acetate—*Sarenin.*

1. Sann L, David M, Richard P, et al: Effect of sodium restriction and angiotensin II infusion in Bartter's syndrome. *Pediatr Res* 10:971-977, 1976.

2. Wald MR, Perrin EV, Bolande RP: Bartter's syndrome in early infancy. *Pediatrics* 47:254-258, 1971.

3. Godard C, Valloton MB, Broyer M, et al: A study of the inhibition of the renin angiotensin system in potassium wastage syndrome, including Bartter's syndrome. *Helv Paediatr Acta* 27:495-512, 1972.

In Reply.—Bartter's syndrome is indeed an intriguing disease to study and we welcome comments such as those of Dr Sann. We found some of his comments confusing. The only similarity between our two articles was that both suggest that some patients with Bartter's syndrome are sodium losers whereas others are not, a fact we documented with ten references in our article. Otherwise, we attempted to separate these two groups (salt losers and non-salt losers) based on biochemical (plasma sodium, potassium, chloride, magnesium, calcium, and bicarbonate levels, renin activity, and blood pH) and historical (age, tetany, and episodes of volume depletion) differences, whereas the article by Sann et al separates the two on the basis of an angiotensin II infusion. Also, we have not found any reference to hypomagnesemia in the communication by Sann et al and assume that their comment on this subject has not yet been published.

We believed that the age difference between our two groups pointed up the possibility that salt losers might eventually become non-salt losers. The findings of both types of Bartter's syndrome in the one family we studied suggested that the etiology of the conditions of the two groups might in fact be similar, the major difference being in kidney maturation or compensation. Thus, sodium losers should be monitored periodically to ensure that any onset of normal renal sodium conservation is detected, "at which time treatment would be altered." However, it must be remembered that this is a syndrome, and therefore there is a possibility of having several etiologies.

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Molybdenum Metabolism

Sir.—We have read with interest the review articles on trace elements in the young infant by Dr Shaw (JOURNAL 133:1260-1268, 1979; 134:74-81, 1980). It is evident that knowledge of trace-element metabolism is of growing importance in the study of many diseases. Although Dr Shaw gives an excellent treatment of some of the well-known trace elements, we would like to comment on his decision to omit a discussion of molybdenum "because so little is known about its role in the metabolism of the fetus and young infant."

A considerable amount of knowledge about molybdenum metabolism in humans has been gained over the past few years. For example, an inverse relationship between copper and molybdenum levels in fetal liver has been established.[1] In addition, it is now known that molybdenum is an essential component of the human.

enzymes sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase.[2] The metal in these enzymes is present in the form of a molybdenum cofactor. The complete structure of this cofactor is not, to our knowledge, known yet, but the presence of a novel pterin moiety in the molecule has been demonstrated.[3]

Recently, a patient's condition has been diagnosed as a combined deficiency of sulfite oxidase and xanthine dehydrogenase.[4,5] The combined deficiency in this individual has been shown to result from an absence of active molybdenum cofactor.[6] The patient has all the clinical symptoms that have been associated with sulfite oxidase deficiency: severe mental retardation, seizures, and bilateral lens dislocation, in addition to many minor dysmorphic features. These symptoms were present almost from birth. Xanthinuria was evident from the presence of small xanthine stones in the urine. Direct clues to the diagnosis were the finding of low plasma uric acid concentrations (0.01 to 0.06 mmole/L) and a positive sulfite test of the urine (Merckoquant Sulfit Test, Merck, Darmstadt, West Germany). Therapeutic trails with oral supplements of ammonium molybdate and inorganic sulfate failed to produce clinical or biochemical improvement.

The patient described above is, to our knowledge, the first person identified with an inborn error in molybdenum metabolism expressed as a combined deficiency of two molybdoenzymes. It is hoped that future studies of this patient will lead to a better understanding of the metabolism and biological function of molybdenum. This information should in turn be of value in better judging the daily requirements for this trace element under normal circumstances and in special situations such as in patients receiving parenteral nutrition.

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1. Meinel B, Bode JC, Koenig W, et al: Contents of trace elements in the human liver before birth. *Biol Neonate* 36:225-232, 1979.

2. Johnson JL: The molybdenum cofactor common to nitrate reductase, xanthine dehydrogenase, and sulfite oxidase, in Coughlan MP (ed): *Molybdenum and Molybdenum-Containing Enzymes*. Oxford, England, Pergamon Press, 1980, pp 345-401.

3. Johnson JL, Hainline BE, Rajagopalan KV: Characterization of the molybdenum cofactor of sulfite oxidase, xanthine oxidase, and nitrate reductase: Identification of a pteridine as a structural component. *J Biol Chem* 255:1783-1786, 1980.

4. Duran M, Korteland J, Beemer FA, et al: Variability of sulfituria: Combined deficiency of sulfite oxidase and xanthine oxidase, in Hommes FA (ed): *Models for the Study of Inborn Errors of Metabolism*. Amsterdam, Elsevier North Holland Press, 1979, pp 103-107.

5. Duran M, Beemer FA, van der Heiden C, et al: Combined deficiency of xanthine oxidase and sulfite oxidase: A defect of molybdenum metabolism or transport? *J Inher Met Dis* 1:175-178, 1978.

6. Johnson JL, Waud WR, Rajagopalan KV, et al: Inborn errors of molybdenum metabolism: Combined deficiencies of sulfite oxidase and xanthine dehydrogenase in a patient lacking the molybdenum cofactor. *Proc Natl Acad Sci* 77:3715-3719, 1980.

In Reply.—I am pleased that Dr Beemer and his colleagues have so promptly plugged the molybdenum gap in my review articles. With hindsight I see it was a serious omission but in writing the review I was conscious that it was turning out very much longer than the editor had requested.

May I take this opportunity of making a correction. The molecular weight of ceruloplasmin has been revised downwards and is thought to be close to 134,000 daltons, and one molecule binds six atoms of copper.[1,2]

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1. Rydén L, Björk I: Reinvestigation of some physiochemical and chemical properties of human ceruloplasmin (ferroxidase). *Biochemistry* 15:3411-3417, 1976.

2. Frieden E, Hsieh HS: Ceruloplasmin: The copper transport protein with essential oxidase activity. *Adv Enzymol* 44:187-236, 1976.

Circumcision

Sir.—In his article in the JOURNAL (134:301-302, 1980), Woodside describes one of the many complications of male circumcision. I applaud his effort to bring it to our attention but I disagree with his conclusion. After detailing the course of fasciitis and sepsis depicting scarified abdomen and genitalia in an infant circumcised on the sixth day of life, he criticizes the technique used and advises a "safer" one.

The Committee on Fetus and the Newborn of the American Academy of Pediatrics, quoted by Woodside, declares that there is no medical indication for routine circumcision in the neonatal period. I submit, therefore, that performance of this procedure—an acknowledged hazard to health—constitutes child abuse. Physicians should prevent, not abet, unhealthful practices.

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In Reply.—I concur that no valid medical indication exists for routine neonatal circumcision and I do not advocate its practice. In reality, however, some parents will continue to request and obtain circumcision for their male infants. Those neonates then deserve to receive a meticulously performed operation, using the safest available technique. In my opinion, Gomco circumcision is the preferred technique.

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Thiamine-Deficiency-Related Cardiac Failure

Sir.—I found the article by Moran and Greene in the February 1979 issue (133:192-199) generally edifying, but wanted to write concerning their recommended management of thiamine-deficiency-related cardiac failure on page 195. They state, "treatment of thiamine deficiency . . . in severe cases 10 mg intravenously . . . resolves . . . cardiac symptoms in 24 to 48 hour. . . . In critically ill adults, 100 mg/day of thiamine parenterally may be necessary."

I believe it would be better to emphasize an approach of initially controlling the cardiac failure by administering digitalis and diuretics. This is because administering thiamine 100 mg intravenously initially might throw the patient into worsening forward failure by increasing metabolic efficiency before the cardiovascular improvement has asserted itself.

I recall a patient seen many years ago in whom a diagnosis of beriberi heart disease was made and who was

given 100 mg thiamine intravenously the night of admission. He died next morning, though he had been in no notable distress on admission. To my recollection, he had had edema for some weeks.

I have not found much on this question in the US literature and would be interested in comments from Greene and Moran. Perhaps a review of the foreign literature would be rewarding.

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In Reply.—When the diagnosis of beriberi heart disease is considered in an individual patient, it should be kept in mind that the genesis of the cardiovascular abnormalities are diverse and a number of variations in initial observation have been recognized.[1] First, there are the classic "wet" forms, in which signs and symptoms of right-sided heart failure with normal or high cardiac output are the initially observed symptoms. Second, a fulminant or "pernicious" variant, termed Shoshin (from the Japanese *sho*, meaning acute damage, and *shin*, meaning heart), may occur with severe biventricular failure, metabolic acidosis, variable cardiac output with vascular collapse, peripheral cyanosis, and death. Treatment of beriberi therefore must be along two main lines: correcting the underlying defect, and treating the clinical manifestations. Obviously, thiamine replacement is the cornerstone of therapy. Treatment of the acidosis with sodium bicarbonate is necessary in critical cases, but it may have only limited success until thiamine replacement is given. Heart failure must be treated with oxygen, diuretics, rest, and salt restriction. Treatment with digitalis, though debatable, is probably justified in acute cases to prevent rapid development of low-output failure and sudden death, as seen in some cases.[2]

In addition to beriberi, other known forms of heart disease may be present in these patients. Recognition of such combinations has obvious therapeutic implications.

Finally, the direct toxic effect of alcohol on the myocardium and the syndrome of alcoholic cardiomyopathy are well known. This is probably one of the causes of persistent cardiomegaly following treatment of beriberi with thiamine.

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1. Seftel HC: Cardiomyopathies in Johannesburg Bantu, Part I: Aetiology and characteristics of beriberi heart disease. *S Afr Med J* 46:1707-1713, 1972.

2. Attas M: Fulminant beriberi heart disease with lactic acidosis: Presentation of a case with evaluation of left ventricular function and review of pathophysiologic mechanisms. *Circulation* 58:566-572, 1978.

Ring Toss

Clarence H. White 1899 From the International Museum of Photography, Rochester, NY

Books

Hemoglobinopathies in Children, edited by Elias Schwartz, 402 pp, with illus, $27.50, Littleton, Mass, PSG Publishing Co Inc, 1980.

The application of recently developed technology to the study of hemoglobin synthesis has led to a sudden expansion of the literature that deals with the hemoglobinopathies and thalassemia. Complete chromosome mapping of the globin genetic regions has been accomplished with bacterial restriction endonucleases, and sequence analysis of DNA and RNA has been facilitated with "probes" of complementary DNA and recombinant technology. As a result, the genetic and molecular flaws underlying disorders of hemoglobin synthesis can be defined with far greater precision than has heretofore been possible. *Hemoglobinopathies in Children,* the third volume in the *Progress in Pediatric Hematology and Oncology* series, is welcomed as a timely synthesis of this newly acquired knowledge. It is authored by 27 persons active in the field and edited by Elias Schwartz, whose clinical and laboratory contributions to the subject are substantial.

The 16 chapters of the treatise are grouped into three sections: normal and aberrant hemoglobin structure and function, the sickling disorders, and thalassemia. Subject material is extensively referenced and interpreted in the light of personal experience. Chapters that are especially well written deserve brief recognition. The discussion of laboratory techniques used for the study of hemoglobin structure and synthesis is succinct and lucid, and provides the uninitiated with a critical appraisal of the relative merits, limitations, and availability of various analyses. The present state of the art of prenatal diagnosis is presented by Blanch Alter with characteristic clarity. Dennis Miller effects a logical synthesis of molecular biology and clinical hematology in a chapter devoted to unstable and functionally anomalous hemoglobins. Outstanding, too, is Temple and Kan's contemporary review of the molecular basis for the thalassemia syndromes.

Surprisingly, some aspects of the subject receive only cursory comment or are omitted altogether. For example, the molecular basis for sickling receives only superficial treatment in a chapter devoted to erythrocyte morphology. The kinetics of sickling, which are of undoubted clinical significance, are not discussed, and an interesting literature concerning irreversible sickling is all but passed over. Because therapeutic considerations are based on extensive personal experience, there is a tendency to slight insights contributed by investigators other than the authors. There is no mention of current efforts to develop clinically useful antisickling agents or of novel approaches to transfusion therapy for thalassemia. Except for the role played by the National Sickle Cell Disease Program, historical aspects of the subject are not reviewed, nor is consideration given the geographical distribution of hemoglobin disorders, population genetics, or prevalence data.

The inclusion of additional illustrative material would have made the reader's task somewhat easier and certainly more enjoyable. The chapter on the molecular biology of thalassemias would have benefited from gene maps to illustrate the differences between β thalassemia, $\beta=\delta$ thalassemia, and hereditary persistence of fetal hemoglobin; and the section dealing with iron overload could use line diagrams that depict iron balance during various therapeutic manipulations. Reproductions of some electron photomicrographs are too dark to permit recognition of key structures, and some of the photomicrographs are magnified unnecessarily.

Despite these annoyances, however, the volume is both readable and authoritative. The editor has successfully circumvented the trap set for all multiauthored texts: excessive duplication of material. The overall high standard of the book assures it a place as a valuable complement to Weatherall and Clegg's *The Thalassemia Syndromes,* published in 1972. The latter is more comprehensive, the former more current. In addition, Schwartz's volume stands alone among books of its kind in its focus on the developmental aspects of the hemoglobinopathies and thalassemia.

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Pediatric Otorhinolaryngology: A Review of Ear, Nose and Throat Problems in Children, edited by Basharat Jazbi, 289 pp, $24.50, New York, Appleton-Century-Crofts, 1980.

The purpose of this book is to "... acquaint pediatricians with the relatively new but important subspecialty and its general role in pediatrics ... the problems are discussed with an orientation to the role of the pediatrician or family practitioner. ..." The book is divided into three major sections (ear, nose, and throat) with chapters on deafness, vertigo, otitis and its complications, epistaxis, sinusitis, choanal atresia, airway ob-

struction, poisoning, tonsillitis and tonsillectomy, and traumatology.

I believe that the book does not fulfill its aim. In fact, the variable style of the chapters (written by multiple authors), their organization (complications and therapy often precede general description and pathogenesis), and the emphasis of the book (20 pages on epistaxis, none on pharyngitis) substantially reduce its value for the student or physician seeking an overview of pediatric otorhinolaryngology.

I am concerned about the lack of balanced presentation of much information: eg, the value of decongestants for systemic effect in therapy of otitis media is stated without qualification despite much recent data to the contrary; no distinction is made between preseptal periorbital cellulitis and orbital cellulitis; only penicillin is discussed in the chapter on treatment of acute otitis media (limited additional discussion occurs in another chapter); laryngotracheoplasty is discussed extensively but there is no discussion of the indications for or management of tracheostomy or nasotracheal intubation; dysmorphology of the face is treated superficially and anecdotally; hearing aids are mentioned in one short paragraph amongst three chapters on deafness.

Despite some chapters of high quality, the majority of this book is a hodgepodge of outdated information, personal opinions and rambling discussion. I cannot recommend it.

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Pediatric Chest Roentgenology: Recognizing the Abnormal, by Webster R. Riggs, Jr, 296 pp, with illus, $37.50, St Louis, Warren H Green Inc, 1979.

This book of nearly 300 pages is intended as an introduction to pediatric chest roentgenology. In chapter 1, the technique of the roentgenographic examination of the chest is illustrated and described, and complementary methods listed. The author prefers the routine of upright posteroanterior and left lateral views of the chest using the Pigg-O-Stat for most infants and uncooperative small children. The device was designed by Mr J. Pigg of Le Bonheur Children's Hospital. Disturbing artifacts produced by the holder margins are illustrated.

In the introduction, the author details the compilation of findings in 1,000 consecutive roentgenographic examinations of the chest over a summer and a winter; that the majority of the examinations were normal motivated his emphasis on "normal chest and borderlands thereof" (chapter 3, 99 pages). Although no new findings are described, among interesting points the author offers is an explanation for the superior extension of the "oblique line" in the superior mediastinum. It probably "consists of posterior layers of pleura above the aortic arch." Many other useful and borderline findings are included.

In chapter 2, the author's philosophy, preferences, and modus operandi for roentgenographic interpretation are offered. The importance of recognizing and effectively dealing with technical imperfections and problems is included. A strong point is made for the value of initially inspecting the roentgenograms unbiased by clinical information. However, for the experienced radiologist, the correlation of other findings with the roentgenographic findings and their interpretation is necessarily biased for the most intelligent opinion. The experience and developed wisdom of the radiologist should be such that he holds his own even in the presence of other biasing influences. The initial inspection and recognition of findings is most important in the training of the radiologist. It probably is less important than the correlative function for the practicing radiologist.

Slightly more than half of the book, chapters 4 through 7, is about the "recognition of the basic departures from normal," findings relevant to the questions "Is there pneumonia? Is there hyperinflation? Is there heart disease?" Again, there are no new concepts, but the text is lucidly and accurately written. In chapter 7, the most commonly encountered abnormalities are presented in the format of a "real life" reading room consultation with the medical student, the resident, the pediatrician, and the radiologist. This scenario is rather folksy and perhaps a little too cavalier for a textbook format, but important diagnostic points for each condition are included.

Overall, there are three photographs and 230 roentgenograms, mostly of adequate if not superior quality. Many only faintly show abnormalities. The references are recent and basic, but not comprehensive.

This book is intended for pediatricians and the general radiologists, but it may be even more valuable as an introductory text for medical students and residents. The author's concepts are sound and he has succeeded in providing a useful introductory text.

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Carbohydrate Metabolism in Pregnancy and the Newborn 1978, edited by Hamish W. Sutherland and John M. Stowers, 540 pp, $32.50, Secaucus, NJ, Springer-Verlag New York Inc, 1979.

This text is a transcription of the second Aberdeen Colloquium, the theme of which titles this book. There are nine general categories, all of which are further subdivided into three to five chapters, ranging from intermediary metabolism of pregnancy to fetal macrosomia to asymptomatic diabetes. The scope of subject matter encompassed is broad and impressive and, almost by necessity, discursive. For example, a chapter devoted to aminoacids and the fetal development of beta cells is immediately followed by the role of glucagon in neonatal hypocalcemia. Despite the title's intimation, *newborn* carbohydrate metabolism is barely addressed but, notwithstanding, the book abounds with discussions of *fetal* metabolism and nutrition. Some sections are almost entirely clinically oriented; for instance, those on the detection of chemical gestational diabetes and the management of maternal diabetes in pregnancy.

Each chapter is well written and sufficiently referenced, ending with the authors' concise summary or comment. This is clearly a reference book for the subspecialist interested in the most recent experimental and clinical advances on the metabolic and somatic adaptations to normal pregnancy, and in particular, the perturbations of the maternal-fetal unit created by diabetes.

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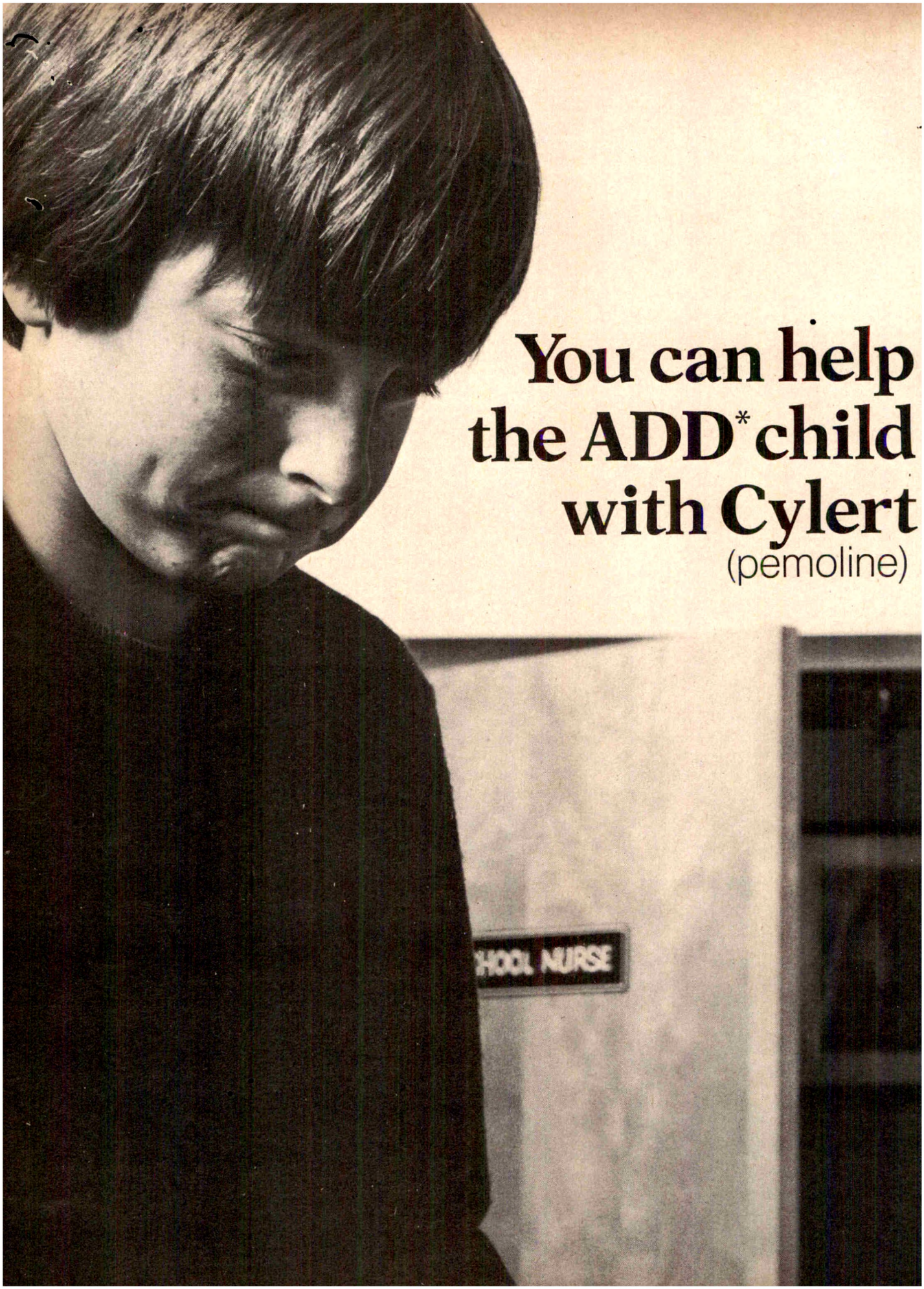

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CLINICAL PHARMACOLOGY: CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS: CYLERT is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms, including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS.)

WARNINGS: CYLERT is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of CYLERT may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with CYLERT is usually not indicated.

Long-term effects of CYLERT in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with CYLERT. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice.)

CYLERT should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of CYLERT with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

CYLERT failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with CYLERT. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. CYLERT should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of CYLERT (pemoline) for use during pregnancy and lactation has not been established.

Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg./kg./day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg./kg./day.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT; it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking CYLERT, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking CYLERT; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of CYLERT: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. A definite causal relationship between CYLERT and these reactions has not been established.

Mild adverse reactions appearing early during the course of treatment with CYLERT often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

OVERDOSAGE: Signs and symptoms of acute CYLERT overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of CYLERT overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg./day. This daily dose should be gradually increased by 18.75 mg. at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with CYLERT is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

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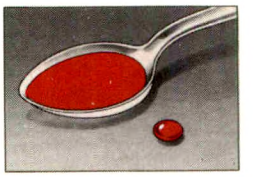

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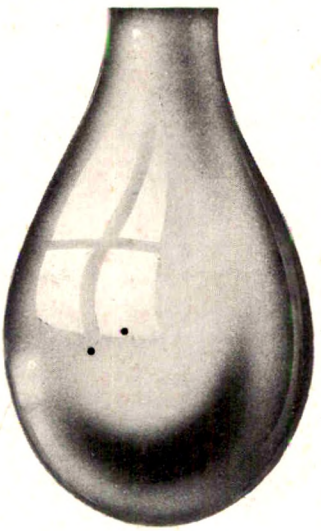

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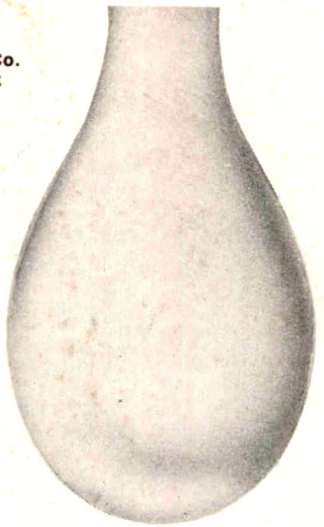

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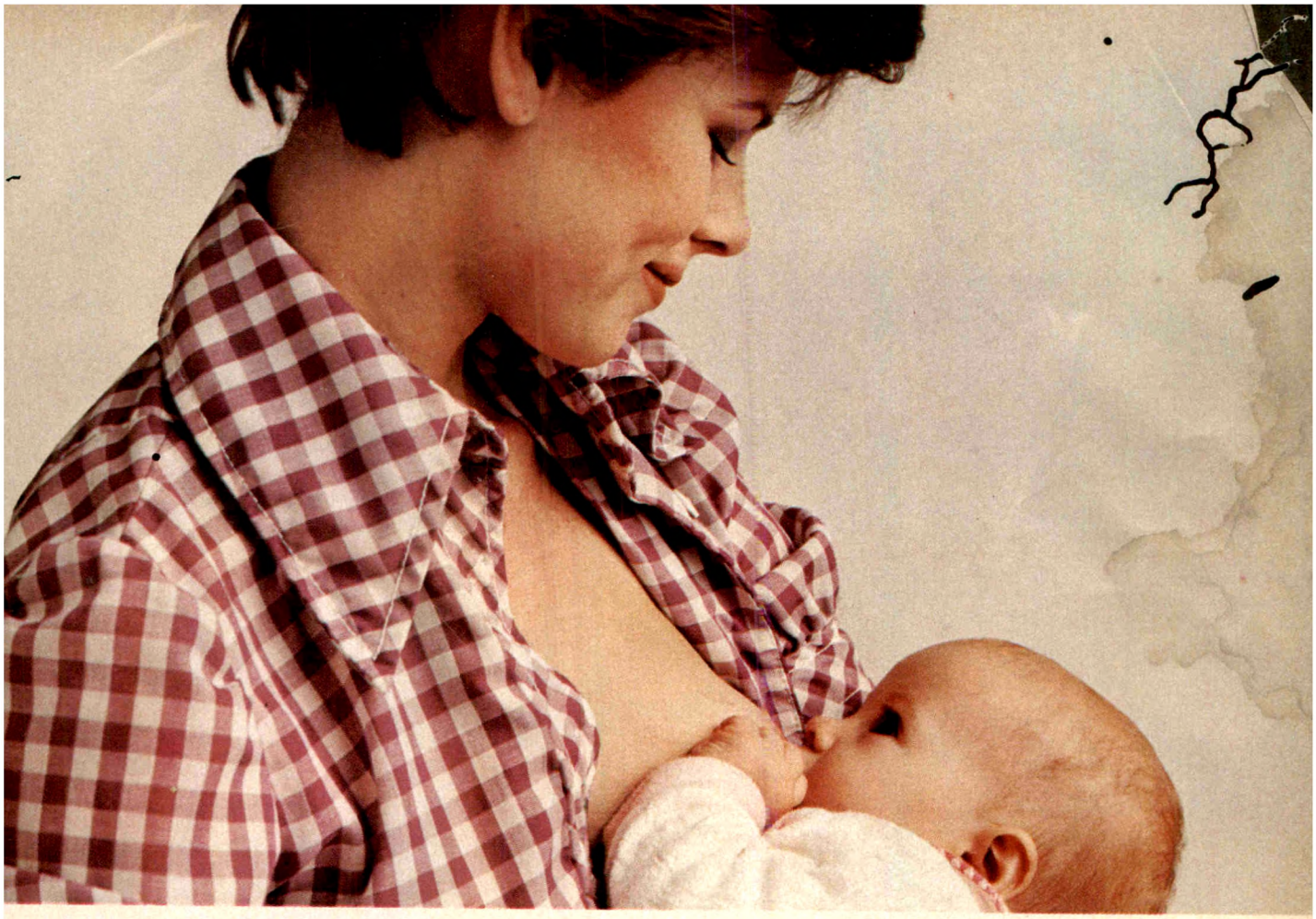

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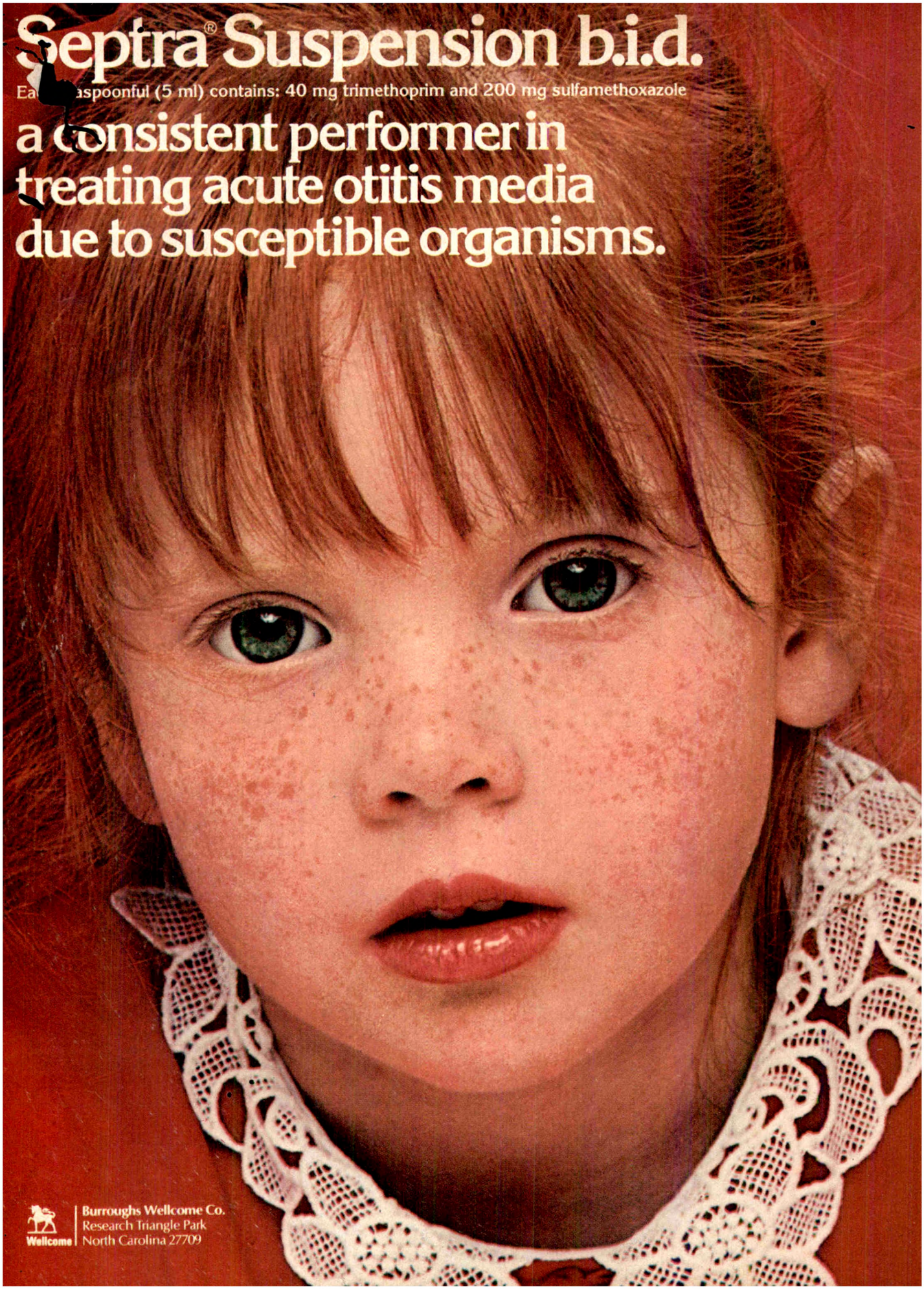
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PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septra may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septra is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. *Blood Dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic Reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal Reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *C.N.S. Reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous Reactions:* Drug fever, chills and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose — every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	½
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1½
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII **PNEUMONITIS:**
The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose — every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	½
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1½
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored — bottle of 473 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

References:

1. Data on file, Burroughs Wellcome Co.
2. Schwartz R, Rodriguez W, Ross S, et al: TMP-SMX in the treatment of otitis media secondary to ampicillin-resistant strains of *H influenzae*. Second International Symposium on Recent Advances in Otitis Media with Effusion, Columbus, Ohio, 1979.
3. Kucers A, Bennett N Mck: *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis*, ed 3. Philadelphia, Lippincott, 1978, p 700.

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Better than ever, as convenient as ever

Single-Dose Vials

M-M-R® II

(MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE | MSD)

Better

contains rubella virus strain RA 27/3

Convenient

one shot vaccinates against all three: measles, mumps, rubella

For a brief summary of prescribing information, please see following page.

MSD
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Indications: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)* — Active immunization against measles (rubeola) in children 15 months of age or older.

BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD) — Simultaneous immunization against rubella and mumps in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling.

MERUVAX®II (Rubella Virus Vaccine, Live, MSD) — Immunization against rubella (German measles) in children 15 months of age to puberty. May be given as early as 12 months if that offers greater convenience in scheduling. May be useful for adolescent and adult males to prevent or control rubella outbreaks in circumscribed population groups. In postpubertal females vaccination must not be undertaken unless the woman is not pregnant, is susceptible to rubella (as shown by Hemagglutination Inhibition test), agrees not to become pregnant for next three months (also in immediate postpartum period), and is informed of frequent occurrence of self-limited arthralgia and possible arthritis beginning two to four weeks after vaccination.

M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD) — Simultaneous immunization against measles, mumps, and rubella in children 15 months of age to puberty.

M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD) — Simultaneous immunization against measles (rubeola) and rubella (German measles) in children 15 months of age to puberty.

MUMPSVAX® (Mumps Virus Vaccine, Live, MSD) — Immunization against mumps for children 15 months of age or older and adults. May be given as early as 12 months if that offers greater convenience in scheduling.

Contraindications: Pregnancy or the possibility of pregnancy within three months following vaccination (see special considerations for ATTENUVAX below); hypersensitivity to neomycin; any febrile respiratory illness or other active infection; for measles-containing vaccines, active untreated tuberculosis; therapy with ACTH, corticosteroids (except as replacement therapy, e.g., for Addison's disease), irradiation, alkylating agents, or antimetabolites; blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary immunodeficiency states, including cellular immune deficiencies, hypogammaglobulinemic and dysgammaglobulinemic states.

Hypersensitivity to Eggs, Chicken, or Chicken Feathers: For measles- and/or mumps-containing vaccines, in patients hypersensitive to eggs, chicken, or chicken feathers, weigh benefits of immunization against potential risks of hypersensitivity reactions.

Pregnancy: *ATTENUVAX* — The effects of ATTENUVAX on fetal development are unknown at this time. Live attenuated measles virus vaccine should not be given to persons known to be pregnant; furthermore, pregnancy should be avoided for three months following vaccination. Reports have indicated that natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects for up to three months following vaccination.

Vaccine administration to postpubertal females entails a potential for inadvertent immunization during pregnancy. Theoretical risks involved should be weighed against the risks that measles poses to the unimmunized adolescent or adult. Advisory committees reviewing this matter have recommended vaccination of postpubertal females who are presumed to be susceptible to measles and not known to be pregnant. If a measles exposure occurs during pregnancy, one should consider the possibility of providing temporary passive immunity through the administration of immune serum globulin (human).

Precautions: Administer subcutaneously; *do not give intravenously.* Epinephrine should be available for immediate use should an anaphylactoid reaction occur. Should not be given less than one month before or after immunization with other *live* virus vaccines, with the exception that ATTENUVAX, MUMPSVAX, and/or MERUVAX II may be administered simultaneously. BIAVAX II may be administered simultaneously with ATTENUVAX. Monovalent or trivalent poliovirus vaccine, live, oral, may be administered simultaneously with ATTENUVAX and/or MUMPSVAX. Vaccinations should be deferred for at least three months following blood or plasma transfusions or administration of more than 0.02 ml human immune serum globulin per pound of body weight. However, rubella vaccine may be given prior to discharge to susceptible postpartum patients who received blood products, provided that a repeat HI titer is drawn six to eight weeks after vaccination to insure seroconversion; similarly, although rubella vaccine may be given in the immediate postpartum period to those nonimmune women who have received anti-Rh_o (D) immune globulin (human) without interfering with vaccine effectiveness, a follow-up postvaccination HI titer should also be determined.

Attenuated measles, mumps, and rubella virus vaccines, live, given separately, may result in a temporary depression of tuberculin skin sensitivity; therefore, if a tuberculin test is to be done, it should be administered before or simultaneously with any of these virus vaccines. Vaccination may not result in seroconversion in 100 percent of susceptible subjects.

Measles-Containing Vaccines — Due caution should be employed in children with a history of febrile convulsions, cerebral injury, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days after vaccination. The occurrence of thrombocytopenia and purpura has been extremely rare.

Rubella-Containing Vaccines — Excretion of live attenuated rubella virus from the nose and throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, is not regarded as a significant risk.

Adverse Reactions: To date, clinical evaluation of the combination vaccines has revealed those adverse reactions expected to follow administration of the monovalent vaccines given separately.

Measles-Containing Vaccines — Occasionally, moderate fever (101–102.9 F); less commonly, high fever (above 103 F); rarely, febrile convulsions. Infrequently, rash, usually minimal without generalized distribution. Reactions at injection site. Local reactions characterized by marked swelling, redness, and vesiculation at the injection site of attenuated live measles virus vaccines have occurred in children who previously received killed measles vaccine; the combination vaccines were not given under this condition in clinical trials.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The Center for Disease Control has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered." However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per thousand reported cases). There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed, far less than the 5 to 10 cases of SSPE per million cases of natural measles.

Rubella-Containing Vaccines — Adverse reactions include malaise, sore throat, headache, fever, and rash; mild local reactions such as erythema, local pain, induration, tenderness, and regional lymphadenopathy; thrombocytopenia and purpura; allergic reactions such as urticaria; and arthritis, arthralgia that is infrequently associated with signs of inflammation, and polyneuritis.

Moderate fever (101–102.9 F) occurs occasionally, and high fever (103 F) occurs less commonly. Rash occurs infrequently and is usually minimal without generalized distribution. Encephalitis and other nervous system reactions have occurred very rarely.

Transient arthritis, arthralgia, and polyneuritis vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. In children, joint reactions are rare and of brief duration if they do occur. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3 percent; women: 12–20 percent), and the reactions tend to be more marked and of longer duration. Rarely, symptoms may persist for a matter of months. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (35–45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

Mumps-Containing Vaccines — Parotitis and orchitis. Rarely, purpura and allergic reactions such as urticaria. Very rarely, encephalitis and other nervous system reactions. With the monovalent mumps vaccine, mild fever occurs occasionally, and fever above 103 F is uncommon.

Shipment, Storage, and Reconstitution: During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10 C (50 F) or less. Before reconstitution, store vaccines at 2–8 C (35.6–46.4 F) and *protect from light.* Use only diluent supplied to reconstitute vaccines. If not used immediately, store reconstituted vaccines in a dark place at 2–8 C (35.6–46.4 F), and discard if not used within eight hours. Use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.

Color: The color of the vaccine when reconstituted is yellow. ATTENUVAX is acceptable for use only if clear.

How Supplied: *ATTENUVAX® (Measles Virus Vaccine, Live, Attenuated, MSD)* — Single-dose vials of lyophilized vaccine, containing when reconstituted not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the FDA Reference Measles Virus, and approximately 25 mcg neomycin.

BIAVAX®II (Rubella and Mumps Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of rubella virus vaccine, live, and 5,000 $TCID_{50}$ of mumps virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Rubella and Mumps Viruses, and approximately 25 mcg neomycin.

MERUVAX®II (Rubella Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than the equivalent of 1,000 $TCID_{50}$ of rubella virus vaccine expressed in terms of the assigned titer of the FDA Reference Rubella Virus, and approximately 25 mcg neomycin.

M-M-R®II (Measles, Mumps and Rubella Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, 5,000 $TCID_{50}$ of mumps virus vaccine, live, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles, Mumps, and Rubella Viruses, and approximately 25 mcg neomycin.

M-R-VAX®II (Measles and Rubella Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, 0.5 ml when reconstituted as directed and containing not less than 1,000 $TCID_{50}$ of measles virus vaccine, live, attenuated, and 1,000 $TCID_{50}$ of rubella virus vaccine, live, expressed in terms of the assigned titer of the FDA Reference Measles and Rubella Viruses, and approximately 25 mcg neomycin.

MUMPSVAX® (Mumps Virus Vaccine, Live, MSD) — Single-dose vials of lyophilized vaccine, containing when reconstituted not less than 5,000 $TCID_{50}$ of mumps virus vaccine expressed in terms of the assigned titer of the FDA Reference Mumps Virus, and approximately 25 mcg neomycin.

Each of these vaccines is supplied as a single-dose vial with a disposable syringe containing diluent and fitted with a 25-gauge, ⅝" needle, and as a box of 10 single-dose vials with an accompanying box of 10 diluent-containing disposable syringes with affixed needles.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

JOVA04

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Instructions for Authors

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Manuscript Preparation.—All the elements of a manuscript must be submitted in **triplicate, double-spaced throughout**. Use heavy-duty white bond paper, 21.6 × 27.9 cm, and 2.5-cm margins. If a word processor is used, do not justify lines. The style of writing should conform to proper English usage and syntax. All measurements are to be in metric units, temperatures in Centigrade.

All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Titles.—Titles should be short, specific, and clear. They should not exceed 42 characters per line, including punctuation and spaces, and be limited to two lines. The title page should include the full names and academic affiliations of all authors, the address to which requests for reprints should be sent, and, if the manuscript was presented at a meeting, the name of the organization, place, and date on which it was read.

Abstract.—Provide an abstract (135-word maximum) of the article, including statement of the problem, method of study, results, and conclusions. The abstract replaces the summary.

Informed Consent.—Manuscripts reporting the results of experimental investigations on humans must include a statement to the effect that informed consent was obtained from the parents or guardians after the nature of the procedure(s) had been fully explained.

Clinical Memoranda.—Brief accounts of interesting observations and clinical situations. Limited to 800 words plus one table or illustration; abstract unnecessary. Submit in triplicate, double-spaced. Copyright assignment required.

Letters to the Editor.—Correspondence pertaining to material published in the JOURNAL. Limit 500 words. Submit in triplicate, double-spaced, and clearly marked "For publication." Copyright assignment required.

References.—List in order of their appearance in the text, and type double-spaced, in the following manner:

1. Applebaum MM, Thaler MM: Reye syndrome without initial hepatic involvement. *Am J Dis Child* 1977;131:295-296.

Do not include unpublished data, personal communications, or manuscripts "in preparation" or "submitted" in the list of references. Such material, if essential, may be incorporated in the body of the article.

Illustrations.—Submit only high-contrast glossy prints in triplicate, unmounted and untrimmed. Preferred size is 12.7 × 17.3 cm (5 × 7 in). Figure number, name of first author, and arrow indicating "top" should be typed on a gummed label and affixed to the back of each illustration. Lettering must be legible after reduction to column size. Magnification and stain should be provided for histologic sections.

For illustrations in full color submit 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies; do not submit color prints. The fee is $275 for up to six square-finished color illustrations that can be arranged on one page. A letter of intent to pay the fee must accompany submission.

Legends.—Legends for illustrations should be typed double-spaced, beginning on a separate sheet of paper (40-word maximum for each).

Acknowledgments.—Illustrations and tables from other publications must be suitably acknowledged, and accompanied by written permission from publisher and author.

Photographic Consents.—A signed statement of consent from **both** parents (or guardian) or the persons involved must accompany all photographs of patients in which a possibility of identification exists. It is not sufficient to cover the eyes to mask identity.

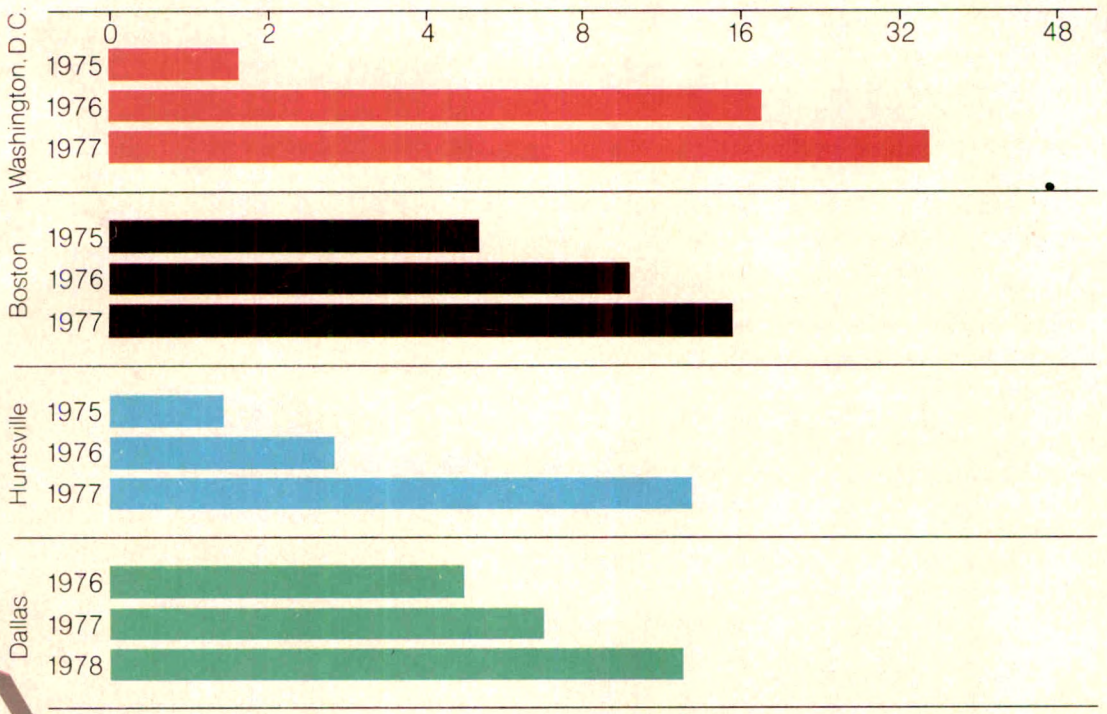
Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 21.6 × 27.9 cm paper. If a table must be continued, use a second sheet and repeat all heads. Each table must have a title.

Uniform Requirements.—Further details on manuscript preparation are given in the document *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* prepared by the International Steering Committee of Medical Editors. Reprints of this document are available by directing requests to this journal: Scientific Publications, 535 N Dearborn St, Chicago, IL 60610.

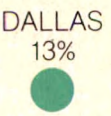
Increasing resistance of

AMPICILLIN RESISTANCE IN HAEMOPHILUS

(Percentages are ampicillin-resistant *H. influenzae* isolates*)



*Isolates obtained from a variety of body fluids (such as middle-ear exudate and blood).



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor*(cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* staphylococci, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor® (cefaclor, Lilly), should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

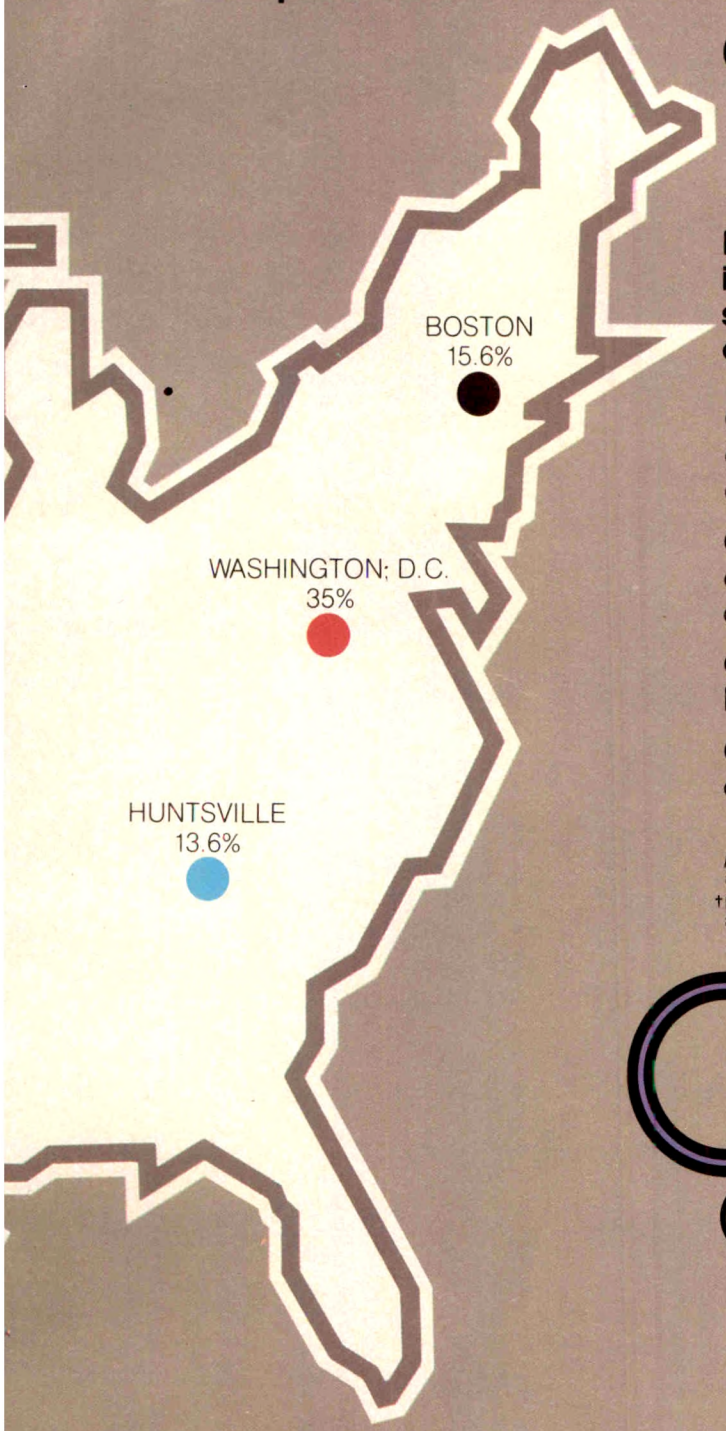
Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side o in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it

Haemophilus influenzae in otitis media...

a valid concern



In many areas of the country, increasing numbers of *H. influenzae* show resistance to conventional antibiotic therapy.[1-3]

Ceclor is effective in the treatment of otitis media†, including that due to some ampicillin-resistant strains of *H. influenzae*.[4-9]

Ceclor has been shown to be clinically and bacteriologically effective in treating otitis media due to susceptible organisms.[10]

Ceclor is available in two pleasant-tasting liquids.

Ceclor provides effective single-agent antibiotic therapy for otitis media.

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

†Due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes*.

125-mg/5-ml and 250-mg/5-ml oral suspensions

Ceclor®

cefaclor

should be recognized that a positive Coombs test may be due to the drug.

Ceclor ® (cefaclor, Lilly) should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: In clinical studies in 1493 patients, adverse effects considered related to cefaclor therapy were uncommon and are listed below:

Gastrointestinal symptoms occurred in about 2.5 percent of patients and included diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions were reported in about 1.5 percent of patients and included morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occurred in less than 1 in 200 patients.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0703799]

References

1. J. Pediatr., *92*:889, 1978.
2. J. Pediatr., *94*:983, 1979.
3. J.A.M.A., *239*:320, 1978.
4. Antimicrob. Agents Chemother., *11*:470, 1977.
5. Antimicrob. Agents Chemother., *13*:584, 1978.
6. Antimicrob. Agents Chemother., *12*:490, 1977.
7. Current Chemotherapy, *II*:880, 1978.
8. Antimicrob. Agents Chemother., *8*:91, 1979.
9. Antimicrob. Agents Chemother., *13*:861, 1978.
10. Data on file, Eli Lilly and Company.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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Mead Johnson
NUTRITIONAL DIVISION

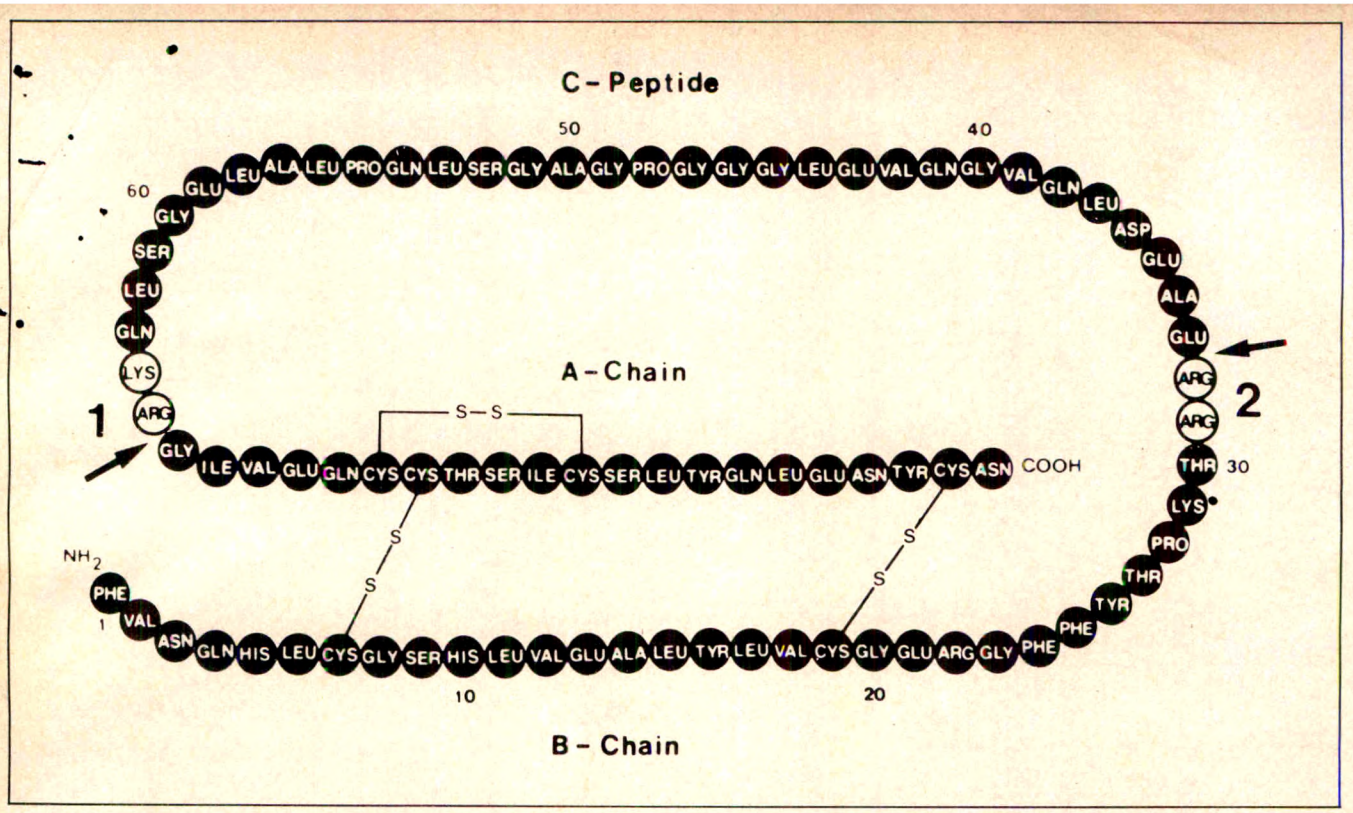
Insulin Biosynthesis and C-peptide

Practical Applications From Basic Research

The insulin molecule released into the circulation by the β cells of Langerhans' islets consists of two separate, straight polypeptide chains linked by disulfide bridges between and within the chains (Figure).[1,2] These two chains are not separately manufactured; instead, the parent molecule synthesized on the ribosome consists of a larger precursor, proinsulin, a single coiled chain in which the amide terminus of the A-chain is linked to the carboxyl terminus of the B-chain by a connecting or C-peptide (Figure).[1,2] Actually, an even larger precursor, pre-proinsulin, containing an additional peptide chain on the amino terminus of the A-chain is initially synthesized. This additional piece acts in a manner analogous to the leader in a film reel and is rapidly excised during synthesis.[1,2] Further processing of proinsulin cleaves the C-peptide consisting of 31 amino acids from the insulin molecule at the sites indicated in the figure. As might be anticipated, defects in the cleavage sites have now been identified.[3-5] That in site 2 in the figure results in familial hyperproinsulinemia, an autosomal dominant defect with no apparent abnormality in carbohydrate metabolism, because the partially cleaved intermediate (B-C proinsulin cleaved at site 1 but not 2) has approximately 50% of the biological activity of insulin. A defect at site 1 also results in an autosomal dominantly inherited disorder of familial hyperproinsulinemia with carbohydrate intolerance of adult-onset diabetes, because the intermediate A-C proinsulin cleaved at site 2 but not at site 1 has less biological activity. Native proinsulin has less than 5%, whereas C-peptide has none, of the biological activity of insulin.[1,2] C-peptide's role appears to be the provision of the spatial arrangements required for the formation of the disulfide bonds.

Under normal circumstances, only a small quantity of proinsulin is released into the circulation, amounting to less than 15% of the total insulin measured by standard radioimmunoassay (RIA).[2] Small quantities of proinsulin intermediates also are released.[2] The greater proportion of proinsulin, however, is cleaved within the β cell into insulin and C-peptide.[1,2] Of most importance is the fact that during insulin secretion induced by various stimuli, one molecule of C-peptide is released with each molecule of insulin. Thus, the plasma of normal persons contains small amounts of proinsulin, proinsulin intermediates, and almost equimolar amounts of insulin and C-peptide. The metabolic half-life of C-peptide is longer than that of insulin; thus, the molar ratio of C-peptide to insulin in peripheral plasma is always greater than one, and the peak of C-peptide secretion or the nadir of its suppression appears to occur later than that of insulin.[6] How can these molecules be distinguished and what practical uses can be made from this distinction?[7]

The standard method now used for measuring insulin in biological fluid is by RIA. The principle underlying this method involves use of an antibody to a hormone and the competition between known and unknown quantity of this hormone to displace in a predictable manner a small amount of the radioactively labeled hormone from this specific antibody. It should be evident from the figure that an antibody to insulin will measure insulin and proinsulin, since the entire insulin molecule is still within its parent structure, but not C-peptide, which is clearly immunologically distinct. Separation of proinsulin from insulin, if desired for research purposes, can be achieved by various procedures such as chromatography to separate the larger proinsulin fraction prior to assay, the use of an enzyme that degrades insulin but not proinsulin, or the use of a C-peptide assay that will measure proinsulin but not insulin.[2] As is apparent from the figure, an antibody specific for C-peptide



Structure of human proinsulin. Arrows 1 and 2 indicate two sites of normal cleavage that yield insulin and C-peptide when arginine (ARG)-31 and -32 residues and ARG-65 and lysine (LYS)-64 residues are removed. During insulin secretion, equimolar amounts of insulin and C-peptide are released. Cleavage sites 1 and 2 are known mutation sites (see text) (from Gabbay[5]).

will measure C-peptide and proinsulin but not insulin. With the C-peptide assay, no interference should theoretically result from the antibodies to exogenous bovine-porcine insulin that develop in all diabetics after a period of insulin treatment.[2] These endogenous antibodies interfere with the RIA for insulin, and their presence confounds the interpretation of results in insulin-treated diabetics.[8] Thus, measurement of C-peptide will reflect β-cell secretory activity even in the presence of antibodies to insulin and will distinguish endogenous insulin secretion, which is accompanied by C-peptide from exogenous insulin administration; in the latter circumstance, there will be no measurable or inappropriately low C-peptide levels, even though RIA shows high insulin values in both circumstances.[8,9] These theoretical considerations form the basis of all practical applications of this assay.[10]

Elsewhere in this issue of the JOURNAL (p 1129), Rappaport et al demonstrate the application of C-peptide measurement to document the persistence of residual β-cell secretory activity in insulin-dependent diabetic children. Those children who could be maintained in good metabolic control as judged from urinary excretion of glucose and levels of glycosylated hemoglobin, despite low doses of exogenous insulin, had substantial residual β-cell function documented by C-peptide measurements. Those children with substantial C-peptide excretion had had their disease for less than one year. Beyond this period of recognized and treated disease, C-peptide excretion fell to negligible amounts, larger doses of insulin were required to maintain metabolic control, and more insulin-binding antibodies developed. Furthermore, residual β-cell function could be documented in many patients recovering from their initial episodes of ketoacidosis.

These findings are not surprising, nor are they really novel. Clinicians have long known that a large proportion of newly diagnosed diabetic children may enter a "honeymoon" period after treatment is first instituted.[8] During this period, the amount of insulin required to maintain apparently excellent metabolic control is remarkably little, and occasionally insulin may be temporarily discontinued. Reduction of insulin dose becomes necessary because of recurrent hypoglycemic episodes. This honeymoon phase lasts for a variable period but seldom longer than one year, and gradually increasing doses of insulin are subsequently required to maintain metabolic control. The use of a standard RIA for plasma insulin levels, performed early in the honeymoon phase after withdrawal of exogenous insulin and before antibodies to the injected insulin could confound the interpretation of results, has confirmed the clinical suspicion that residual insulin secretory activity must be present, at least early after diagnosis.[8,11] Consequently, in the period after initial diagnosis, C-peptide assays do not provide any more useful information in the management of the case than clinical response of the patient and the clinical acumen of the physician. Nevertheless, the C-peptide assay has proven to be an excellent research tool with which to document the extent and duration of residual β-cell function despite the develop-

ment of insulin antibodies.[7,8,10] However, precautions must be taken not to overestimate the magnitude of residual β-cell function. Antibodies to exogenous insulin will bind endogenous proinsulin and impair its degradation and metabolic clearance. Proinsulin will, as indicated above and as is evident from the figure, react in the C-peptide assay so that C-peptide levels may be spuriously high.[7] With appropriate methodologic precautions, however, careful studies using C-peptide have demonstrated that some residual β-cell function may persist for up to five years after diagnosis. These studies also demonstrated that "brittle" diabetes is almost always associated with near-total lack of insulinogenic reserve but that the reverse is not true; good control can be achieved by exogenous insulin despite absence of endogenous insulin reserve.[12] The article by Rappaport et al in this issue reaffirms and highlights all of these points. Most provocative of all is the claim by Danish workers that early diagnosis before the onset of severe ketosis, followed by intensive insulin treatment to normalize metabolism, increases the likelihood of preserving endogenous insulin production as reflected in C-peptide levels, which in turn facilitates diabetic control.[7,13] This "research" finding imposes some powerful obligations on the practicing physician. As a research tool, C-peptide has provided irrefutable evidence of residual β-cell function not only in diabetics but also of excessive insulin secretion in infants born to diabetic mothers.[14] In these infants, the maternal antibodies to administered insulin cross the placenta, producing interference in the measurement of the infant's serum insulin level by RIA.

It is not in diabetes but rather in the differential diagnosis of hypoglycemia that C-peptide measurement has its most practical application. In all forms of spontaneous hypoglycemia except insulinoma, endogenous insulin secretion, and therefore C-peptide secretion, decreases. When blood glucose concentration falls below 40 mg/dL, insulin secretion is curtailed, so that serum insulin concentration is low and usually less than 10 μU/mL. If, at the time of hypoglycemia, serum insulin concentration is inappropriately high, determination of C-peptide levels permits differentiation between an insulinoma and factitious hyperinsulinemia as a result of self-administered insulin.[15] In the former, C-peptide levels are high and at least equimolar to insulin levels, reflecting endogenous secretion, whereas in the latter, C-peptide levels will be low or absent, reflecting curtailment of endogenous insulin secretion by the exogenous insulin. When factitious hypoglycemia is suspected, including this possibility as a manifestation of child abuse, the triad of low plasma glucose, high immunoreactive insulin, and suppressed C-peptide levels is pathognomonic of exogenous insulin administration. And, in cases of suspected insulinoma where spontaneous hypoglycemia may occur only intermittently, it is no longer necessary to employ provocative maneuvers such as prolonged starvation to provoke hypoglycemia and to simultaneously measure insulin levels; the problem of having a physician or nurse on hand precisely when the hypoglycemic episode occurs is well known to those who have used this procedure. With the availability of C-peptide measurement, it is possible to rapidly exclude insulinoma as the cause of the hypoglycemia by means of an intravenous bolus (0.1 unit/kg) or infusion (0.1 unit/kg for one hour) of insulin. C-peptide levels will fall as hypoglycemia develops from the injected insulin but will not appropriately fall in patients with insulin-secreting tumors.[9,16] Indeed, the standard, two-hour, arginine-insulin tolerance test used by endocrinologists to evaluate pituitary function will provide information on all forms of hormone deficiency (growth hormone, cortisol, glucagon) or hormone excess (endogenous insulin-C-peptide) that might be responsible for the hypoglycemia.[17] If all results are normal, a nonhormonal cause of hypoglycemia is implicated. Obviously, these tests should be performed under strict medical supervision by physicians familiar with the procedure, with glucose readily available.

It has been over 50 years since the discovery of insulin, but only in the past 15 years have studies elucidated some details of its structure, biosynthesis, and function. Complete understanding of insulin's mechanism of action is still lacking; however, insulin continues to be the model for understanding hormone synthesis and its disorders. This understanding provides new insight into the causes of diabetes and practical application to diagnose various disorders of carbohydrate metabolism. The applications of C-peptide, of which the report by Rappaport et al is but one example, reflect the harmonious interplay between basic scientific research and its clinical applications.

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References

1. Steiner DF: Insulin today. *Diabetes* 26:322-340, 1977.
2. Kitabchi AE: Proinsulin and C-peptide: A review. *Metabolism* 26:547-587, 1977.
3. Steiner DF: Errors in insulin biosynthesis. *N Engl J Med* 294:952-953, 1976.
4. Gabbay KH, DeLuca K, Fisher JN, et al: Familial hyperproinsulinemia: An autosomal dominant defect. *N Engl J Med* 294:911-915, 1976.
5. Gabbay KH: The insulinopathies. *N Engl J Med* 302:165-167, 1980.
6. Faber OK, Hagen C, Binder C, et al: Kinetics of human connecting peptide in normal and diabetic subjects. *J Clin Invest* 62:197-203, 1978.
7. Binder C, Rubenstein AH: Proceedings of an International C-peptide Research Symposium. *Diabetes*, suppl 1, 1978, pp 145-285.
8. Block MB, Rosenfield RL, Mako ME, et al: Sequential changes in β-cell function in insulin-treated diabetic patients assessed by C-peptide immunoreactivity. *N Engl J Med* 288:1144-1148, 1973.
9. Liljenquist JE, Horwitz DL, Jennings AS, et al: Inhibition of insulin secretion by exogenous insulin in normal man as demonstrated by C-peptide assay. *Diabetes* 27:563-570, 1978.
10. Horwitz DL, Kuzuya H, Rubenstein AH: Circulating serum C-peptide. *N Engl J Med* 295:207-209, 1976.
11. Johansen K, Orskov H: Plasma insulin during remission of juvenile diabetes. *Br Med J* 1:676-678, 1969.
12. Shima K, Tanaka R, Morishita S, et al: Studies on the etiology of 'brittle diabetes.' *Diabetes* 26:717-725, 1977.
13. Ludvigsson J, Heding LG, Larsson Y, et al: C-peptide in juvenile diabetics beyond the post-initial remission period. *Acta Paediatr Scand* 66:177-184, 1977.
14. Sosenko IR, Kitzmiller JL, Loo SW, et al: The infant of the diabetic mother. *N Engl J Med* 301:859-862, 1979.
15. Scarlett JA, Mako ME, Rubenstein AH, et al: Factitious hypoglycemia. *N Engl J Med* 19:1029-1032, 1977.
16. Service FJ, Horwitz DL, Rubenstein AH, et al: C-peptide suppression test for insulinoma. *J Lab Clin Med* 90:180-186, 1977.
17. Burstein S, Velayo NL, Sperling MA: C-peptide response to arginine stimulation and insulin suppression demonstrates low insulin reserve in growth hormone deficiency, abstracted. *Pediatr Res* 14:475, 1980.

New Evidence on Food Additives and Hyperkinesis

A Critical Analysis

The Feingold diet continues to be a matter of controversy. In this MARGINAL COMMENT, *Dr Esther Wender discusses the findings of two studies recently reported in* Science. *Rebuttals by the authors of these two studies follow in sequence.*—ED.

Just at a time when Feingold-diet watchers in the scientific community have concluded that his food-additive-free diet is of little or no proven value in the treatment of hyperactivity and learning disability (unpublished data presented at the Conference on Nutrition and Behavior, Franklin Institute of Philadelphia, Williamsburg, Va, March 10-12, 1980),[1] two articles published in a recent issue of *Science*[2,3] have stimulated further comment that this dietary treatment is effective (*New York Times*, April 1, 1980, p C1; *Science News*, March 29, 1980, pp 199, 204). The April 9 edition of *Pediatric Notes*,[4] for example, reports briefly on these two articles and then concludes, "The Feingold diet is in with a bang. It doesn't matter how you view these studies, it seems quite clear that food dyes will have to go." It most certainly does matter how one views these studies, and this is why a brief review of both reports is the topic of this MARGINAL COMMENT.

The first investigation was by Weiss et al,[3] who studied 22 preschool-aged children recruited through advertisements requesting volunteers who had already been treated with the food-additive-free diet and had responded favorably. Both the treatment and the report of favorable response had been based on uncontrolled, informal clinical trials. These children were not selected to meet criteria for the diagnosis of either learning disability or the hyperactivity syndrome. All of them displayed behaviors that were troublesome to their parents, but no diagnostic evaluation was attempted. The patient population, therefore, was not necessarily either hyperactive or learning disabled and the group was highly selected on the basis of previously reported improvement on the food-additive-free diet.

These 22 children were then placed on a strict Feingold diet, which excluded the preservatives butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) as well as the usual exclusion of foods containing artificial colors and flavors and foods said to contain natural salicylates. (The children had already been on less strictly managed food-additive-free diets.)

They were then challenged daily for eight consecutive weeks with either a mixture of artificial food colorings or a placebo that contained no artificial colorings and was indistinguishable from the active challenge. The food-coloring challenge was given once each week on randomly assigned days. The mixture contained 35 mg of food coloring, which was considered to be the average amount consumed in an *entire day* by young children. Behavior was observed primarily by the parents, who listed target symptoms at the beginning of the study and rated these targeted behaviors on each challenge day. When teachers were available, they also rated target symptoms. Outside observers periodically made home visits to check on the accuracy of parent reports, but for each family this occurred infrequently. As long as the challenges are truly indistinguishable from each other, subjective parent ratings should not consistently favor one kind of challenge over the other.

In only one child did most of the target behaviors seem worse at the time of the active challenge as compared with the placebo challenge. Because that child was very young (2 years 10 months), school observations were not available. In one other child, the authors reported equivocal changes of doubtful clinical substance. Without independent corroboration, the results in this one child cannot be accepted as good evidence of a relationship between food colorings and behavior for two reasons: first, in two other studies,[5,6] there were similar reports of behavioral change by a parent, but in both of these studies, other observations were available and did not confirm the parents' report; second, independent corroboration is necessary to ensure that the parents' report is not based on their ability to distinguish between the active and the placebo challenge, a distinct possibility since the presence of artificial colorings can be detected by a technique known as "kitchen chromatography." This refers to a separation of colors that can be seen when the food that contains the mixture of artificial colorings is mixed with water and allowed to soak into an absorbent napkin or towel.

The authors state that the aim of their study was "simply to determine if behavioral sensitivity to color additives could be demonstrated in a controlled trial" and not to estimate prevalence. Yet Dr Weiss is reported to say, in response to questions about this study, that "Even if only one percent of children are affected, that's still a lot of children" (*New York Times*, April 1, 1980, p C1). What he fails to mention is that these 22 children represent a very highly selected group who were already considered to have improved with dietary treatment, and that 21 of them, previously identified as Feingold-diet responders who deteriorated consistently with dietary infractions, failed to demonstrate that pattern when the dietary challenge was administered in a placebo-controlled fashion.

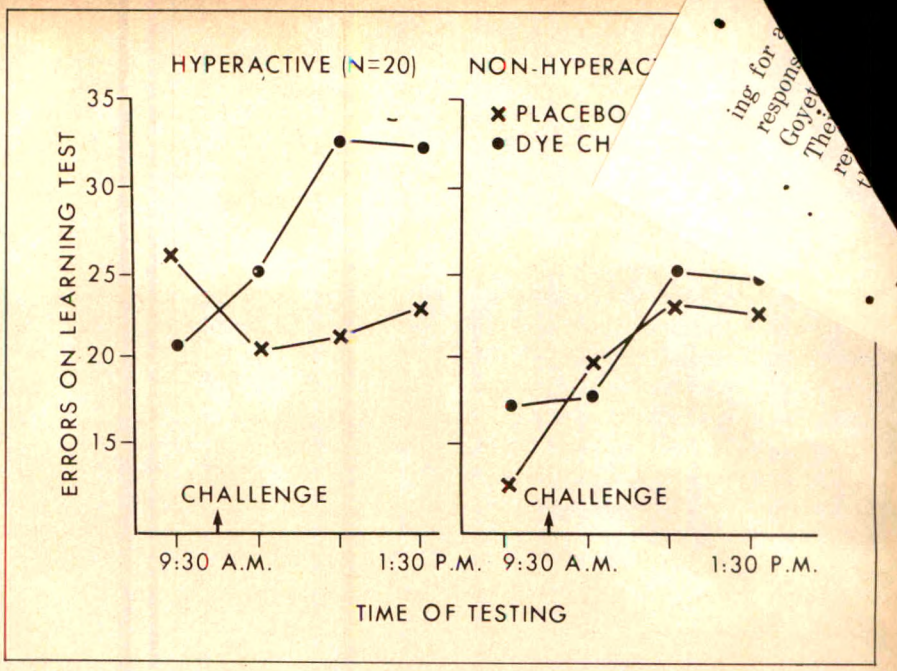
The second study is reported by Swanson and Kinsbourne and stems from research conducted at the Research Institute at the Toronto Hospital for Sick Children.[2] These investigators did not directly evaluate the hypothesis generated by Dr Feingold. For example, this was not a study of the effects of food additives on behavior even though Dr Feingold claims that his diet produces behavioral change. Instead, they studied the effects of food colorings on a laboratory task that measures the ability to sustain attention. Swanson and Kinsbourne measured behavioral change in

this and earlier studies but found no differences between the active and placebo challenges.

In this study, children were placed on the Feingold diet and were then challenged with a mixture of artificial food colorings in doses of 100 and 150 mg, given as a bolus in an opaque capsule. The authors state that the larger dose is at the 90% level for the amount of food coloring ingested by children in an *entire day* according to the food-coloring intake survey made in preparation for the study of Weiss et al.[3] This amount is far in excess of the dose likely to be ingested with the dietary infractions described by Feingold and others.

The study population consisted of two groups of school-aged children whom Swanson and Kinsbourne call "hyperactive" and "nonhyperactive" based on their response to stimulant medication. They measured medication response by the child's performance following the administration of a single dose of medication on a laboratory task that measures the ability to sustain attention. Once they divided their patients into favorable and adverse medication responders, they summarized the scores on the ten questions of the Conners Teacher Questionnaires that correlate most highly with a diagnosis of hyperactivity and found that the favorable responders yielded an average score of 16 and the adverse responders yielded a mean score of 12.6. On these ten questions, a score between 0 and 9 is within normal range and a score of 15 is 2 SDs above the mean. The 12.6 mean score of the adverse responders is therefore definitely higher than average but does not reach 2 SDs above the mean.

The designations hyperactive and nonhyperactive based on these criteria are very misleading. Diagnosis of the behavioral syndrome often called hyperactivity is based primarily on a history of at least two years' duration both at school and at home of excessive activity and restlessness, impulsiveness, and inattention and distractibility.[7] Though the Conners questionnaire ten-item score often correlates with hyperactivity as indicated by history, the questionnaire cannot replace the history as a diagnostic tool. Also, a favorable response to



Responses of hyperactive children and nonhyperactive children challenged with food-dye blend or with placebo (from Swanson and Kinsbourne[2]).

medication does not establish, and an adverse response does not preclude, the diagnosis. The group that these authors call nonhyperactive might better be described as "less hyperactive."

Swanson and Kinsbourne demonstrated a statistically significant increase in the number of errors made 1½ and 3½ hours after the food-coloring challenge compared with the placebo challenge, but only in the hyperactive group. If one looks, however, at their data, there appears to be a striking difference in the placebo performance between the two groups (Figure). In the nonhyperactive group, the error rate at baseline was low and gradually rose with repeated testing. This pattern would be expected since children fatigue with frequent testing. By contrast, in the so-called hyperactive group, the error rate at baseline was at its highest and then dropped following the placebo challenge. The reason for those different patterns of placebo response in the two groups is not apparent. Swanson et al, in other articles using the same laboratory task, obtained placebo-response patterns like that seen in the nonhyperactive children.[8] The *pattern* of response seen after both the active challenge and the placebo challenge in the nonhyperactive group was very similar to the pattern seen after the active challenge in the hyperactive children but at a higher rate in this latter population, as would be expected since they were more symptomatic. Because of the unusual placebo-response pattern in the so-called hyperactive group, this study needs to be replicated before the results can be accepted.

It is unfortunate that these two articles are being cited as supporting the claim that artificial food colorings play a substantive role in producing symptoms of hyperactivity. The study of Weiss et al[3] actually provides some of the most convincing evidence that food colorings have nothing to do with the improvement in behavior seen by parents when their children are placed on the Feingold diet. All 22 of the children in this study were, according to their parents, dramatic diet responders who deteriorated with dietary infractions. Yet when they were fed, under double-blind conditions, large doses of food coloring (much more than would be consumed in any ordinary diet infraction), no such deterioration was seen, except in one child where the change in behavior was noted only by the mother.

In the Swanson and Kinsbourne study,[2] no *behavioral* change was noted even with food colorings given at doses of 100 and 150 mg. They therefore turned to a laboratory task, look-

short-lived pharmacological e that had been described by te et al in an earlier report.[9] r' method of testing involved peated tests over short periods. In his situation, both practice and fatigue . effects must be taken into account. Since they found differences between the active and placebo challenges only in the more symptomatic group and since those differences are associated with an unexpected pattern of placebo response seen in that group, their results must be replicated before they can be accepted. Conners et al attempted to replicate Swanson's findings but found no consistent differences between the placebo and the food-coloring challenge.[10] In summary, the Swanson and Kinsbourne study showed none of the behavioral changes that Dr Feingold stresses, and the findings on the laboratory learning task cannot be accepted until the unexpected placebo response is explained.

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References

1. *Final Report: Summary of Research,* The National Advisory Committee on Hyperkinesis and Food Additives. New York, The Nutrition Foundation Inc, 1980.
2. Swanson JM, Kinsbourne M: Food dyes impair performance of hyperactive children on a laboratory learning test. *Science* 1980;207:1485-1487.
3. Weiss B, Williams JH, Margen S, et al: Behavioral responses to artificial food colors. *Science* 1980;207:1487-1488.
4. Gellis SS: Editorial. *Pediatric Notes* 1980; 15:57-58.
5. Mattes J, Gittelman-Kelin R: A crossover study of artificial food colorings in a hyperkinetic child. *Am J Psychiatry* 1978;135:987-988.
6. Harley JP, Matthews CG, Eichman P: Synthetic food colors and hyperactivity in children: A double-blind challenge experiment. *Pediatrics* 1978;62:975-983.
7. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III),* ed 3. Washington, DC, The American Psychiatric Association, 1980, pp 41-44.
8. Swanson JM, Kinsbourne M, Roberts W, et al: Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. *Pediatrics* 1978;61:21-29.
9. Goyette CH, Conners CK, Petti TA, et al: Effects of artificial colors on hyperkinetic children: A double-blind challenge study. *Psychopharmacol Bull* 1978;14:39-40.
10. Conners CK: *Food Additives and Hyperactive Children.* New York, Plenum Press, 1980, chap 6.

In Rebuttal

In her discussion of a recent article by us[1] on the effect of food dyes on hyperactive children, Dr Wender raises an interesting point about the performance of our subjects during the day following challenges with placebo. She claims that the differences in performance between the dye and placebo conditions can be accounted for by an "unexpected pattern of response" by the hyperactive group of subjects in the placebo condition, and she recommends that our results be seriously questioned until this unexpected response is explained. In fact, for the procedures used in our study and data analysis, the pattern of performance in the hyperactive group after a placebo challenge is virtually identical to the pattern we reported earlier,[2] and it is the pattern of the nonhyperactive (or less hyperactive) group that differs from our previous report. Thus, the *opposite* of Dr Wender's claim may be true for our data.

What does this mean with respect to her comment on our findings? Following her logic, we should accept the presence of a dye-induced effect in the hyperactive group since we have explained the pattern of response in the placebo condition, which she challenged, but we should *not* accept the lack of a dye-induced effect in the nonhyperactive group since they were the ones who manifested an unexpected pattern of response in the placebo condition. Of course, we do not believe that this is reasonable, nor do we believe that Dr Wender would draw this conclusion. Thus, we present the following discussion to address the question she has posed.

Dr Wender's confusion about the expected and unexpected pattern of performance after a placebo administration is understandable, since a subtle methodological difference in how the data are analyzed determines the expected pattern. We have discussed this in detail elsewhere.[2] When the data from individual subjects in the placebo condition are taken directly without an adjustment for baseline, as was done in our article,[1] then in the group averages a pattern reflecting an initial improvement from the first to the second test, followed by a gradual deterioration across subsequent tests, is to be expected (see Kinsbourne et al,[2] Fig 4). However, when the initial score of the day is used to adjust the subsequent scores of each subject to reflect percentage change from baseline,[3] then only a pattern of gradual deterioration appears in the group averages representing performance after an administration of placebo (see Kinsbourne et al,[2] Table 1). The different appearance of the group curves for these two procedures is due to the differential weighting of scores for extreme subjects by these methods when the data from individual subjects are combined.[2]

What pattern would emerge if we did adjust for baseline? If we were to use an average baseline score across the two challenge days and adjust for baseline according to procedures we have used before,[3] than the effect of the food-dye challenge would be magnified in the hyperactive group since the initial score in the placebo condition is higher than the initial score in the food-dye condition (see Swanson and Kinsbourne,[1] Fig 1a).

Despite the difficulty in establishing the expected pattern of performance after placebo administration in our study on food dyes, the implication of Dr Wender's point is valid: the two groups (the hyperactive and nonhyperactive in our terminology, or the more hyperactive and the less hyperactive in her terminology) do seem to differ in the pattern of performance following placebo administration. We have performed an alternative decomposition of the three-way interaction reported in our

article (involving patient type, challenge, and test time) to verify this difference. Instead of performing a simple effects analysis of the within-subject factor (challenge and test time), which is the preferred procedure and the one reported in our article,[1] we analyzed the effects of one between-subject factor (patient type) and one within-subject factor (test time) for the placebo condition and the food-dye condition separately.

In this simple effects analysis of the placebo data, the interaction of the two factors (patient type and test time) was significant ($F(3,108) = 5.45$, $P < .01$), confirming Dr Wender's point that the pattern of performance for the two groups did differ in the placebo condition. A further decomposition of this significant two-way interaction revealed that the two groups differed *only on the first test*, which was given before the challenge was administered, and that no group differences occurred for the three tests given after the challenge. We have no explanation as to why the two groups differed on the first test within the placebo condition, but we should point out that the variation across the two challenge days for performance on the first test was not significant for either the hyperactive or the nonhyperactive group. The average performance for the subjects in the hyperactive group was worse in the placebo condition than in the food-dye condition, but the difference (−5.9 errors) failed to reach statistical significance (see Swanson and Kinsbourne,[1] Table 1). The average performance for the nonhyperactive subject was better in the placebo condition than in the food-dye condition, but again the difference (+4.2 errors) was not statistically significant.

When the data from the food-dye condition and the placebo condition are analyzed separately, the effect of the type of challenge (dye or placebo) cannot be evaluated directly in the simple effects analysis of the factors of patient type and test time for the data from these two conditions treated separately. Of course, this is why we chose to perform the other decomposition of the three-way interaction in our original article.

If the problematic data from the first test are not considered, the significant effect of the food-dye challenge on the later tests remains. Or, if a nonparametric analysis is used (as we reported in Table 1 of our article[1]), the statistically significant effect of the challenge with food dye remains. Furthermore, we stand behind our procedure for decomposing the significant three-way interaction in our original report. We believe that Dr Wender's opinion qualifies as a post-hoc comparison of a set of data in which a variety of tests or comparisons can be made. However, if the established procedures of analysis of variance are followed (which are designed to prevent the investigator from focusing on spurious or chance differences), then the question posed by Dr Wender would be unlikely to receive serious consideration. Even if it is considered, our conclusions remain unchanged.

Another problem in Dr Wender's comments on our article concerns her reference to Conners' use of our learning test in a study of the effects of food dyes on hyperactive children.[4] He used challenges of 26 mg of food dye and found no significant differences between dye and placebo challenges. This replicates our earlier finding for 26-mg challenges[5]; only when we went to much larger challenges (100 mg and 150 mg) did we find significant effects.[1] Conners[4] describes his data as being suggestive of an acute effect of food dye and he states with "20-20 hindsight" that he should have increased the amount of dye in the challenges to maximize the chance of eliciting a response. This is the main point of our article in *Science*, which our last sentence reinforces: "When a blend of dyes is used, a high dose may be necessary to elicit a behavioral response in hyperactive children."[1] We see no reason for our results to be seriously questioned on the basis of Conners' study, as suggested by Dr Wender, since his results are consistent with our earlier findings.[5]

Dr Wender has an important point to make in her marginal comment, and the readers of the JOURNAL deserve to have it clearly stated to prevent misunderstanding. The results of the two articles in *Science*[1,6] do not confirm all (or even most) of the claims made for the Feingold diet. They were not designed for that purpose. In fact, two of the findings (that only two of 20 children showed any response to food-dye challenges in the study of Weiss et al[6] and that no behavioral response was documented by rating scales in our study[1]) can be used to argue against the hypothesis that a large dose of food dye will dramatically affect in the short term the behavior of hyperactive children. On the other hand, the statistically significant effects of food dyes reported by Weiss et al[6] and by us[1] cannot be discounted, and they do provide some limited support for the aspects of the Feingold hypothesis that they were designed to test. To put the positive and negative aspects of these two studies into perspective, it is not necessary to attempt to discredit the statistics or the data from these studies in order to ignore their positive aspects. It is effective and accurate to point out the narrow focus and negative aspects of these studies, and then to interpret the positive results in that context.

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References

1. Swanson JM, Kinsbourne M: Food dyes impair performance of hyperactive children on a laboratory learning test. *Science* 1980;207:1485-1487.

2. Kinsbourne M, Swanson JM, Herman D: Laboratory measurement of hyperactive children's response to stimulant medication, in Denhoff E, Stern L (eds): *Minimal Brain Dysfunction: A Developmental Approach*. New York, Masson Publishing Co, 1979, pp 81-106.

3. Swanson JM, Kinsbourne M, Roberts W, et al: Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. *Pediatrics* 1978;61:21-29.

4. Conners CK: *Food Additives and Hyperactive Children*. New York, Plenum Press Inc, to be published.

5. Swanson JM, Kinsbourne M: Artificial color and hyperative behavior, in Knights RM, Bakker DJ (eds): *Treatment of Hyperactive and Learning Disabled Children*. Baltimore, University Park Press, 1980, pp 131-149.

6. Weiss B, Williams JH, Margen S, et al: Behavioral responses to artificial food colors. *Science* 1980;207:1487-1488.

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In Rebuttal

David P. Rall, Director of the National Institute of Environmental Health Sciences and of the National Toxicology Program, once challenged an audience with the following question: Suppose that thalidomide, rather than inducing structural deformities, had instead depressed IQ scores by 10%; would we ever have suspected it of adverse effects?

The answer to that question is disquietingly obvious. Rall framed it to illustrate the problems now taunting the science of environmental toxicology. Absence of death and frank disease are too blunt to serve alone as evidence of safety. The community demands protection against the subtle, insidious, often delayed consequences of exposure to toxic environmental agents, consequences exemplified by behavioral disturbances. Behavioral toxicology is a discipline created by that concern. Although a young discipline—the first meeting was organized in 1972[1]—it is exerting a widening influence. In the Toxic Substances Control Act of 1976, which mandates premarket toxicity evaluation of all new chemicals introduced into commerce, Congress specified behavior as one of the salient criteria. Japan and Great Britain now require behavioral toxicity evaluations of new drugs. And the current anxieties stirred by obstetric medications and alcohol consumption during pregnancy center on their enduring behavioral consequences.

The study that my collaborators and I conducted[2] grew out of that perspective. Our aim was not to estimate prevalence of sensitivity to food colorings but simply to determine if behavioral measures could detect doses normally consumed by children. We did not test the Feingold diet as therapy. We did our study because the issue of behavioral toxicity from food additives far transcends in societal importance the role of Feingold's elimination diet as therapy.

To review the study, 15 male and seven female children, 3 to 7 years old, composed the sample. None suffered from notable medical or psychiatric problems. Almost all subjects were solicited through the Kaiser-Permanente system (not by advertisements). All had been eating an elimination diet for at least three months before entering the study and, according to parents, had shown improvement in problem behaviors on the diet. The experiment lasted 11 weeks. On every day of that period, the child consumed a specially formulated bottle of soft drink. The first three weeks and last week constituted baseline periods. On eight randomly determined days during weeks 3 through 10, the drink contained a blend of seven certified food colors instead of the control preparation. On every day of the study, the parent participant recorded counts and ratings of ten individualized target behaviors, completed the Conners ten-item Parent-Teacher Questionnaire, and performed several other associated duties.

We had to labor under several limitations. First, we administered a dosage, 35.6 mg/day, that we calculated from a survey as the mean daily intake of children between 1 and 6 years old who were enrolled in the Kaiser-Permanente system. Restrictions imposed by human-subject review committees precluded tests of higher doses. Furthermore, we administered this dose only once weekly, on the average. Yet some children may consume as much as 184 mg daily, the Food and Drug Administration estimate of mean daily consumption is 75 mg, and other experiments[3] suggest a dose-response relationship. Second, it would have been statistically advantageous to challenge on more than eight occasions,[4] but 11 weeks is a long period for parents whose lives are constrained by a demanding protocol. Third, trained observers, whose reliability could be quantified, might have given us more sensitive indices of response, but their cost could have easily doubled our budget. Our observers visited once weekly (not "infrequently"). These limitations curtailed the sensitivity of the experiment. Despite them, we detected two responders. One, a 3-year-old boy, showed significant enhancements of the two target behaviors claimed by his mother as those most pronounced after previous dietary infractions. The other, a 34-month-old girl, showed significant elevations on five of the seven aversive target behaviors, on the Conners Questionnaire, and on other indices.

Dr Wender contends that these results were either due to the ability of parents to detect the dye blend or else may represent a statistical artifact. Her insinuations about "kitchen chromatography," however, are invalid. As we noted, the control and challenge drinks were "indistinguishable by sight, smell, taste, or *stain color*." We were aware of that problem; we solved it, as reported, by preparing a freeze-dried monoblend of the seven colors (which yielded a more uniform stain) and, because our blend left a pink stain, by adding varying concentrations of cranberry coloring to both drinks to foster maximum confusion. I am astonished by Dr Wender's assertion because she had access to our FDA report, which described these precautions in detail. I also described this procedure and its development at a small meeting in January 1979 that Dr Wender cochaired. Perhaps she was confused by my narration of our attempts to deter kitchen chromatography. The data also contradict her hypothesis. Not all indices responded equally to challenge, as our figures demonstrated. Not all indices, moreover, responded equally on any particular challenge day. Any knowledgeable experimenter would expect far more uniformity had the code been breached.

Dr Wender's second objection is quasistatistical, that is, one mild and one cogent case in 22 children cannot be adduced as evidence of behavioral sensitivity to food dyes. This objection betrays an unfamiliarity with both statistics and toxicology. Dr Wender seems unaware of certain critical statistical implications of the Feingold hypothesis. Nowhere does Feingold claim that all children respond favorably to the diet or adversely to food dyes. A population, however, composed of both susceptible and resistant persons reduces the chances of

finding a statistically significant response of the group to treatment and violates the assumptions underlying conventional statistical models. Assume, for example, a sample population containing 30% responders. If a treatment shifts the mean of the responders by 1 SD, it would take samples of 265 subjects from that population to attain consistent statistical significance. Such problems are now being addressed by statisticians in contexts ranging from responsiveness to antibiotic treatment[5] to the impact of air pollution on asthmatics[6] to the Feingold hypothesis. A human population is not a jar of jelly beans.

Dr Wender makes other misleading allegations. For example, her first sentence asserts that "Feingold diet watchers" had concluded that his diet was of little value. Which watchers? Her first reference, to a workshop on nutrition and behavior, perplexes me because I was one of the organizers of that meeting and chaired the section on toxicology. She was not present. Her second reference is a document sponsored by the Nutrition Foundation, but she is one of its authors, and a consultant to the Foundation. It is also incorrect that we attempted no diagnostic evaluation of the children. They were thoroughly examined by Kaiser-Permanente pediatricians and, if necessary, by psychiatrists and psychologists (as we have reported). Dr Wender also tends to equalize our challenge study with the total Feingold diet. Coloring elimination is only one component of that diet. And, to stress again, we challenged only intermittently with the mean daily dose. Our study design would not detect cumulative effects.

Dr Wender's position also reflects an uncritical appraisal of the literature. Two controlled trials of the total diet have demonstrated statistically significant improvements in treated children. One reported an incidence of 50% (23/46).[7] Another observed improvement in four or five of 15 subjects.[8] A coloring challenge study detected adverse consequences in about 25% of a sample of 24 children.[9] Dr Wender's interpretation of the study of Swanson and Kinsbourne[3] also reflects confusion. After denying any action of food dyes or the elimination diet on "learning disabilities," she dismisses as irrelevant an experiment that demonstrated learning deficits after dye ingestion. She doesn't grasp the fact that learning is an aspect of behavior. She describes the task used by Swanson and Kinsbourne[3] as merely a test of attention without, apparently, realizing that now hyperkinesis is considered an attention deficit disorder.

The most dismaying feature of Dr Wender's critique, however, is her insensitivity to the toxicological issues. Food additives are not now tested for behavioral toxicity.[10] Safety is gauged mainly by absence of detectable pathologic conditions.[11] From feeding studies in rodents, toxicologists typically calculate a "no-effect level," then divide by a 100-fold safety factor to determine an allowable daily intake, the amount that presumably can be ingested without harm.[12] My statement about the importance of a 1% incidence was made in that context. Even that incidence denotes a zero safety factor, because the allowable daily intakes for food dyes greatly exceed the quantities evoking behavioral effects. Dr Wender's statements about the "excess" quantities ingested within a limited time are also misdirected. Without more knowledge of food-dye pharmacokinetics and amounts in food, we do not know if it is an important issue. Thirty grams of ice cream or 100 g of a carbonated beverage may contain as much as 10 mg of tartrazine.[13]

Safety factors are especially critical for the developing organism. As readers of the JOURNAL are distinctly aware, the immature nervous system is more sensitive to many toxic agents than is the adult nervous system, sometimes exquisitely so. Methylmercury is only one compelling example.[14] The Feingold literature offers a disturbing parallel. All ten of a group of preschool-age hyperactive boys responded positively to an elimination diet.[7] The youngest subjects in an early color challenge study proved to be the most sensitive.[15] The two detected responders in our experiment were also among the youngest. Neonatal rats display behavioral abnormalities when given a blend of food colors at a dose approximating ours.[16]

Behavioral teratology designates that branch of behavioral toxicology whose focus is the functional aftermath of perinatal toxic exposure. Given the enhanced sensitivity of the fetus and neonate to so many other agents, should not prudent clinicians caution pregnant and nursing women and parents of young children about the conspicuous absence of behavioral data in food-additive safety testing, as well as the balance of risks and benefits? Food dyes are cosmetic additives and serve no crucial nutritional function. Growing restrictions on food dyes by other governments,[13] coupled with the expanding role of behavioral assessment in toxicology, indicate that Dr Wender's complacency is far from universal.

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References

1. Weiss B, Laties VG: *Behavioral Toxicology.* New York, Plenum Publishing Co, 1975.
2. Weiss B, Williams JH, Margen S, et al: Behavioral responses to artifical food colors. *Science* 1980;207:1487-1488.
3. Swanson JM, Kinsbourne M: Food dyes impair performance of hyperactive children on a laboratory learning test. *Science* 1980;207:1485-1487.
4. Glass GV, Willson VL, Gottman JM: *Design and Analysis of Time-Series Experiments.* Boulder, Colo, Colorado Associated University Press, 1975.
5. Good PI: Detection of a treatment effect when not all experimental subjects will respond to treatment. *Biometrics* 1979;35:483-489.
6. Whittemore AS, Korn EL: Asthma and air pollution in the Los Angeles area. *Am J Public Health* 1980;70:687-696.
7. Harley JP, Ray RS, Tomasi L, et al: Hyperkinesis and food additives: Testing the Feingold hypothesis. *Pediatrics* 1978;61:818-828.
8. Conners CK, Goyette CH, Southwick DA, et al: Food additives and hyperkinesis: A controlled double-blind experiment. *Pediatrics* 1976;58:154-166.
9. Williams JI, Cram DM, Tausig FT, et al: Relative effects of drugs and diet on hyperactive behaviors: An experimental study. *Pediatrics* 1978;61:811-817.
10. Evaluation of health aspects of GRAS food ingredients: Lessons learned and questions unanswered, Federation of American Societies for

Experiemental Biology Select Committee on GRAS Substances. *Fed Proc* 1977;36:2525-2562.
11. Weiss B: Food additives, in Committee on Nutrition (ed): *Pediatric Nutrition Handbook*. Evanston, Ill, American Academy of Pediatrics, 1979, pp 454-464.
12. Toxicological evaluation of certain food additives with a review of general principles and of specifications, Joint Food and Agriculture Organization-World Health Organization Expert Committee on Food Additives. *WHO Tech Rep Ser* No. 539, 1974.
13. Berglund F: Food additives. *Arch Toxicol Suppl* 1978;1:33-46.
14. Amin-Zaki L, Majeed MA, Elhassani SB, et al: Prenatal methylmercury poisoning: Clinical observations over five years. *Am J Dis Child* 1979;133:172-177.
15. Goyette CH, Conners CK, Petti TA, et al: Effects of artificial colors on hyperkinetic children: A double-blind challenge study. *Psychopharmacol Bull* 1975;14:39-40.
16. Shaywitz BA, Goldenring JR, Wool RS: Effects of chronic administration of food colorings on activity levels and cognitive performance in developing rat pups treated with 6-hydroxydopamine. *Neurobehav Toxicol* 1979;1:41-47.

Is There an Optimal Time to Schedule Residency Interviews?

The process of applying for a primary care residency position has become increasingly complicated in recent years. Some senior medical students seem to spend an inordinate amount of time and energy on this effort that may begin at the end of their junior year and extend up until the deadline for the National Resident Matching Program (NRMP) during the first week of January. The prospective applicant generally schedules interviews with five to ten programs that often vary in size, geographic location, and university or community affiliation. Larger residency programs may set up predetermined interview days, whereas smaller programs tend to schedule interviews at the convenience of the applicant.

Does it matter when the prospective applicants schedule their interviews? Applicants say that they are told, usually by faculty advisors or fellow students, that interviews should not be scheduled too early in the course of the academic year for fear that they will have been forgotten by the time the rank order of applicants is transmitted to NRMP. Other students are advised not to come too late for fear that program directors might believe that they have not demonstrated sufficient interest in their particular program.

We studied whether the date of the applicant's interview for a residency position affected his or her rank order for the NRMP.

MATERIALS AND METHODS

All applications (excluding those from our own students) to the Pediatric Residency Program of the Upstate Medical Center, Syracuse, NY, for the five-year period of 1974 to 1978 were reviewed. In each year, applicants were divided into four groups by their numerical NRMP ranking: group 1, top 20; group 2, 21 to 40; group 3, 41 to 60; and group 4, 61 or greater. The dates of the applicant interviews were recorded by months: July-August, September, October, November, and December.

Ranking of Residency Applicants by Month of Interview

	Ranking Group*				
Applicant Interview	**1**	**2**	**3**	**4**	**Total†**
July-August	6	11	6	4	**27**
September	8	8	11	12	**39**
October	16	28	32	28	**104**
November	28	26	31	32	**117**
December	15	14	9	21	**59**
Total	**73**	**87**	**89**	**97**	**346**

*Ranking group indicates numerical National Resident Matching Program ranking: group 1, top 20; group 2, 21 to 40; group 3, 41 to 60; and group 4, 61 or greater.
†Applicants from Upstate Medical Center, Syracuse, NY, excluded.

COMMENT

The data from the applicant record review are given in the Table. Each cell of the Table represents the number of applicants in the four ranking groups by month of interview during this five-year period. No trend in ranking by month of interview is noted by perusal of the Table. A χ^2 test for $r \times c$ tables was 12.95 with 12 *df*, giving a probability of approximately .4. There were no significant differences in the ranking categories by the month of interview, which demonstrates that the timing of the interview was neither an advantage nor a disadvantage in the applicant's ultimate ranking.

Despite this finding, we have noted a striking change in the time that applicants come for interview. In 1974, 13 students visited our program in the summer months, while in 1978 only one student was interviewed during that period. Similarly, there has been a drop in applicants seen in December, from 14 in 1974 and 21 in 1975, to four in 1978. October and November have been the peak months of visitation for four of the past five years. Scheduling all applicants during this limited time period has become more difficult.

The timing of the program interview for residency, at least in the pediatric department at the Upstate Medical Center, does not affect subsequent ranking for the NRMP. Interviews should be scheduled at the convenience of both the applicant and the program.

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Marginal Comments

Urine C-peptide, β-Cell Function, and Insulin Requirement

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• Urinary C-peptide excretion was investigated as a method for monitoring β-cell function in diabetic patients and for studying the contribution of endogenous insulin production to diabetic control. Control subjects had variations in serum and urine C-peptide immunoreactivity that correlated with basal and meal-related insulin secretion. In a group of well-controlled juvenile diabetic patients, those receiving high doses of insulin had low or negligible C-peptide excretion, whereas most patients with low exogenous insulin requirements had near-normal urinary C-peptide excretion. Patients treated for diabetic ketoacidosis had recovery of β-cell function as measured by C-peptide immunoreactivity in serial urine specimens. Thus, measurement of urinary C-peptide excretion is a simple technique that may be useful in assessing endogenous insulin production in juvenile diabetic patients.

(*Am J Dis Child* 134:1129-1133, 1980)

From the Departments of Pediatrics (Drs Rappaport, Ulstrom, and Fife) and Laboratory Medicine and Pathology (Drs Hedlund and Steffes), University of Minnesota School of Medicine, Minneapolis; and the Department of Pediatrics, St Louis Park Medical Center, St Louis Park, Minn (Dr Etzwiler). Dr Rappaport is now with the Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of Beth Israel Hospital, Department of Medicine, Beth Israel Hospital and Harvard Medical School, Boston.

Reprints not available.

Development of an assay for C-peptide in serum and urine has allowed investigation of endogenous insulin production in persons with diabetes mellitus who are receiving exogenous insulin. In 1973, Block et al[1] determined, by measuring serum C-peptide immunoreactivity, that the remission period characterized by improved carbohydrate tolerance and diminished insulin requirement in some juvenile diabetics was the result of renewed β-cell activity. Other workers have confirmed, by measuring both fasting and stimulated serum C-peptide concentrations, that patients with juvenile diabetes have significant endogenous insulin production.[2-7] These data were gathered using serum samples and could be obtained only in a hospital or clinic. They provided information on C-peptide secretion during a limited period.

Measurement of C-peptide immunoreactivity in the urine has been proposed as a method for obtaining integrated data on β-cell function in diabetic patients.[8,9] We undertook to establish the validity of urine C-peptide measurement as an index of β-cell function by simultaneous assessment of serum insulin and C-peptide and urine C-peptide levels in a group of normal adults. We made similar measurements in three children with juvenile-onset diabetes during a three-hour oral glucose tolerance test.

For editorial comment see p 1119.

In nine patients with juvenile-onset diabetes, we measured 24-hour urine C-peptide excretion. These data were correlated with daily insulin dose, duration of clinical diabetes, and qualitative assessment of insulin-binding antibody concentrations in serum. We also measured urine C-peptide excretion in three patients during episodes of diabetic ketoacidosis.

SUBJECTS

These investigations were approved of by the University of Minnesota (Minneapolis) Committee on the Use of Human Subjects in Research. Informed consent was obtained from control subjects and from patients and/or their parents.

Control Subjects

Six healthy subjects, three men and three women ranging in age from 19 to 33 years and each being within 10% of ideal body weight, participated in the study. There was no history of diabetes mellitus in first-degree relatives of any of these subjects.

Following a dietician's instructions, sub-

jects consumed diets containing at least 200 g of carbohydrate daily for three days prior to hospitalization. Subjects were admitted to the Clinical Research Center the day before the 24-hour test period, during which time they received three equicaloric meals at 7:30 AM, 12:30 PM, and 5:30 PM. Total calories were appropriate for height, weight, and age. Fluid intake during the test period was 2 to 3 L. Only water was allowed between meals. Subjects were permitted free activity on the ward.

Blood samples for glucose, C-peptide, and insulin concentrations were obtained via an indwelling needle at half-hour intervals beginning a half hour before breakfast and continuing for 24 hours. Serum was separated and frozen (−20 °C) in aliquots for later assay. Urine was collected in timed fractions (two to five hours' duration) throughout the day and overnight.

Ten healthy children of hospital personnel served as control subjects for total 24-hour urine C-peptide excretion. Their ages ranged from 3 to 14 years. Their urine was collected at home. No effort was made to regulate diet or physical activity during these collections.

Juvenile Diabetic Patients

Three children (aged 4, 5, and 14 years) were discovered to be diabetic because of polyuria and polydypsia without ketoacidosis. Prior to initiation of insulin therapy, all three underwent three-hour oral glucose tolerance tests with simultaneous measurement of serum insulin and C-peptide and urinary C-peptide excretion.

In three patients (aged 15, 16, and 23 years), urinary C-peptide excretion was studied during episodes of ketoacidosis. The condition of two of the three was newly diagnosed, and that of one had been diagnosed eight months prior to the time during which he was studied.

In nine juvenile-onset diabetic patients who were 4 to 20 years old, 24-hour urinary C-peptide excretion was measured. They had clinical diabetes of two months' to 7½ years' duration. Their insulin doses were 11 to 47 units/sq m/24 hr (0.3 to 1.5 units/kg/24 hr) (Table 1). These insulin doses were determined by the patients' primary physicians and were not adjusted for the purposes of this study. Eight of the nine followed their normal daily living patterns during the time of study. One was hospitalized for investigation of his low insulin requirement. Subjects selected were known to be in good diabetic control. Each was studied only if the total 24-hour urine glucose excretion on the day of study was less than or equal to 5% of the daily carbohydrate intake. The adequacy of these selection criteria was substantiated by measurement of glycosylated hemoglobin concentrations in seven of the nine patients. At the end of the 24-hour collection period, blood was drawn for measurement of serum creatinine and glycosylated hemoglobin levels (except in patients 6 and 8).

METHODS

C-peptide immunoreactivity in urine and serum was measured using a double-antibody radioimmunoassay (RIA) kit (Calbiochem) for human C-peptide that uses rabbit antiserum prepared against synthetic human C-peptide, iodine I 125-tyrosylated synthetic human C-peptide, and synthetic C-peptide standard. Goat antirabbit γ-globulin is the precipitating antibody. Urine samples were diluted as necessary with the assay buffer, 1% bovine serum albumin in 0.01M phosphosaline with 0.05M ethylenediaminetetraacetic acid (EDTA), having a pH of 7.6, and 0.01% thimerosal. The sample volume was 200 μL, and the total volume in each assay tube, 900 μL. The lower limit of sensitivity of the assay was 0.5 ng/mL ($P < .01$). Dilution of the urine with buffer did not alter the measured urine C-peptide content.

Urine samples were collected in glass or plastic containers and kept refrigerated during the collection period. Sodium hydroxide (1N) was added to samples to adjust the pH to 7 to 8. Samples were centrifuged to remove sediment, and aliquots were kept frozen until analyzed.[8] Urine and serum creatinine levels were measured by the alkaline picrate method.[10]

Glycosylated hemoglobin concentration was measured by a technique similar to that of Trivelli et al.[11] Whole blood (collected with heparin or EDTA as an anticoagulant) was centrifuged. From 50 to 100 μL of packed blood cells was transferred to a 1.5-mL centrifuge tube and mixed with an equal volume of lysing solution (0.1M potassium cyanide containing 1% octoxynol-9 [Triton X-100]); 1.2 mL of buffer 1 (33 mM sodium biphosphate, 8.3 mM sodium phosphate, 10 mM potassium cyanide) was added and the tube was mixed again. The tube was then centrifuged in a microcentrifuge (Eppendorf). The clear supernatant fluid was added to a column containing a cation exchange resin (Biorex-70) (70 × 100 mm) and the glycosylated hemoglobins were eluted with 30 to 35 mL of buffer 1. The slow fraction was eluted with 20 to 25 mL of buffer 2 (1.4 mM sodium biphosphate, 46 mM sodium phosphate). The optical density of each fraction was measured at 415 nm after fivefold dilution of the slow hemoglobin fraction. The amount of glycosylated hemoglobin was expressed as a fraction of the total eluted hemoglobin. Our normal range for glycosylated hemo-

Clinical Data of Nine Diabetic Subjects

Patient No./ Age	Duration of Diabetes	Insulin Dose, Units/sq m	Glycosylated Hemoglobin,* % of Total	Creatinine Clearance, mL/min/1.73 sq m	Urine C-Peptide,† μg/sq m/ 24 hr	Serum Total Insulin, μg/mL	Serum Free Insulin, μU/mL
1/11 yr 2 mo	4 yr 6 mo	47	10	150	Negligible	2,100	16
2/10 yr	5 yr	32	9.6	92	Negligible	4,200	8
3/10 yr	7 yr 6 mo	27	8	121	Negligible	2,300	12
4/7 yr 10 mo	2 yr	27	10.6	82	4.5	4,100	6
5/4 yr	3 yr	15	8	89	Negligible	660	6
6/12 yr	10 mo	14	. . .	117	32	59	28
7/11 yr 6 mo	7 mo	13	11.1	103	14	45	4
8/20 yr	7 mo	11	. . .	. . .	38	. . .	. . .
9/13 yr 2 mo	2 mo	11	9.9	160	53	360	34

*The mean normal value (± 1 SD) was 6.2% (± 1.0%) (n = 51).
†The range was 19 to 92 μg/sq m/24 hr (n = 10).

globins measured by this method (6.2% ± 1.0%) is in close agreement with the range obtained by other groups.[11,12] Patients judged clinically to be in fair or poor control had a mean glycosylated hemoglobin concentration of 15.2% ± 1.5%.

Serum free and total insulin concentrations were measured according to the method of Nakagawa et al,[13] except that the volumes used were one fifth those employed in the originally described assay. Urine glucose concentration was estimated with copper sulfate tablets (two-drop Clinitest method).[14] Serum insulin levels were measured by a modification of the double-antibody method of Morgan and Lazarow.[15]

Mean values of serum insulin (μU/mL) and C-peptide (ng/mL) levels were computed for each period of urine collection in normal subjects. Similar calculations were made for the duration of the three-hour glucose tolerance tests in three diabetic patients. A best-fit line and correlation coefficient relating serum to urine C-peptide levels were computed using data from all control subjects (inset, Fig 1).

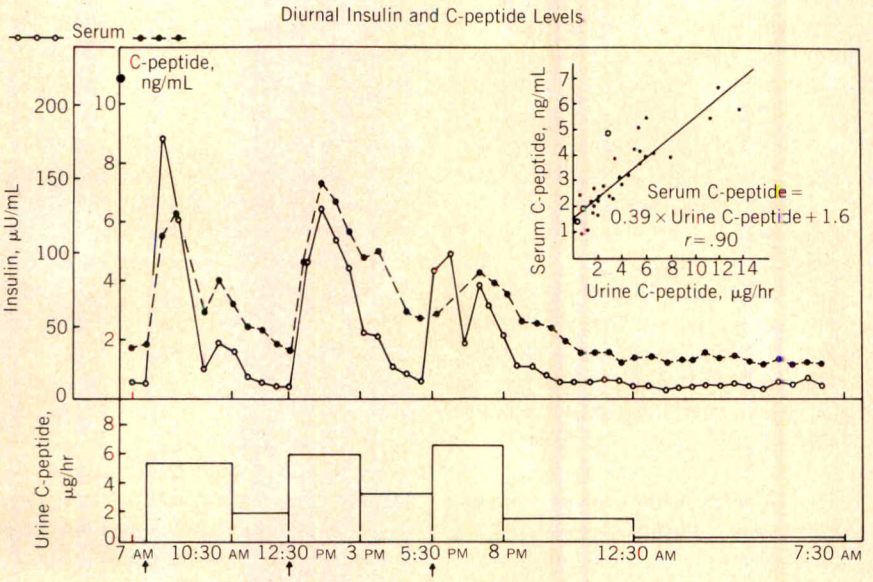

Fig 1.—Representative 24-hour profile of control subject's serum insulin and C-peptide concentrations and urinary C-peptide excretion. Arrows designate meal times. Inset, Relationship of mean serum C-peptide level to hourly urinary C-peptide excretion of control subjects (closed circles) and of three diabetic children (open circles) ($P < .001$).

RESULTS

Control Subjects

In the six adults, urinary C-peptide excretion rose sharply immediately after meals, diminished during postabsorptive periods, and for each period studied correlated well with the mean serum C-peptide concentration (Fig 1). The ten children had a mean urinary C-peptide excretion of 39 μg/sq m/24 hr, with a range of 19 to 92 μg/sq m/24 hr.

Juvenile Diabetic Patients

For the three patients who underwent oral glucose tolerance tests, points representing urinary C-peptide excretion during the three-hour test plotted against mean serum C-peptide concentration during the same period correlated well with data obtained from the control subjects (inset, Fig 1). In addition, serum insulin and C-peptide levels rose and fell synchronously throughout the test.

All patients with ketoacidosis were initially treated with continuous low-dose insulin infusions (< 0.1 units/kg/hr). Within 24 hours, they were

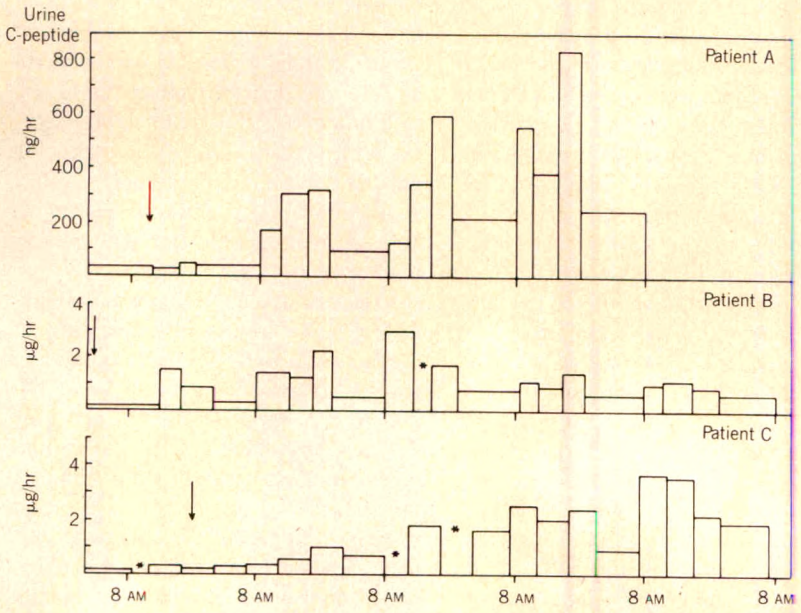

Fig 2.—Urine C-peptide excretion during and following therapy for diabetic ketoacidosis in three patients. Arrows indicate clearing of urine ketones and resumption of normal diet. Asterisks designate times when no urine was obtained.

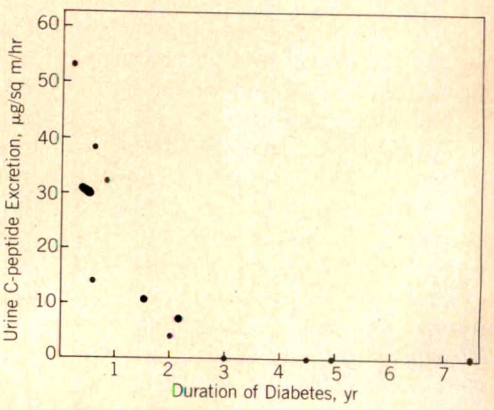

Fig 3.—Relationship of 24-hour urinary C-peptide excretion to duration of clinical diabetes mellitus.

eating meals normally and receiving intermittent subcutaneous short-acting, or a combination of short- and intermediate-acting, insulin. Urinary C-peptide excretion rose within 24 to 48 hours after the initiation of therapy (Fig 2). All subjects demonstrated higher urinary C-peptide excretion during the day, when they were eating, than during overnight periods of fasting. With resolution of ketoacidosis, the meal-related changes in excretion of C-peptide demonstrated in control subjects were reestablished in the diabetic patients.

In nine patients studied, 24-hour urinary C-peptide excretion was related to insulin dose and duration of diabetes. Of four patients receiving insulin doses of 27 to 47 units/sq m/24 hr, three had negligible urinary C-peptide excretion (Table). One (patient 4) had a measurable but low urinary C-peptide excretion of 4.5 μg/sq m/24 hr. All of these four patients had diabetes of relatively long duration (Fig 3). The remaining five patients were receiving low doses of insulin, 11 to 15 units/sq m/24 hr. Four of these had measurable urinary C-peptide excretion. Measurements of three were in the same range as those of the control subjects studied. The remaining patient (5), who differed from the others in that he had diabetes of long duration, had negligible urinary C-peptide excretion (Table).

Creatinine clearance was normal in two of the eight patients in whom it was measured. Two patients (1 and 9) had elevated creatinine clearances, and four patients (2, 4, 5, and 7) had slightly diminished creatinine clearance compared with age-appropriate normal values (Table).[16] There was no correlation between creatinine clearance and C-peptide excretion.

Serum free and total insulin concentrations were measured in eight of the nine patients to obtain a qualitative estimate of insulin-binding antibodies. Four of the five patients with diabetes of long duration had high serum total insulin values indicative of substantial insulin-binding antibodies. The fifth child (patient 5) had a lower serum total insulin value and required an insulin dose of only 15 units/sq m/24 hr (0.6 units/kg/24 hr). Of the four patients with clinical diabetes of less than one year's duration, serum total insulin concentration was measured in three. All had levels much lower than those found in patients with clinical diabetes of long duration (Table).

COMMENT

In normal and diabetic subjects in this study, mean serum C-peptide concentrations correlated well with simultaneous urinary excretion of C-peptide. Measurement of urine C-peptide in two- to three-hour collections reflected acute changes in β-cell secretory response to meals. Thus, assessment of urinary C-peptide excretion provided a potentially useful measure of β-cell activity.

We applied this technique to two groups of patients: three patients with diabetic ketoacidosis and nine well-controlled juvenile diabetics. In the first group, studied longitudinally during and immediately after episodes of ketoacidosis, there were substantial increases in urinary C-peptide excretion within 24 to 48 hours after correction of ketoacidosis. Although collection periods were not optimal for revealing acute, meal-related increases in urinary C-peptide excretion, there were fluctuations in urinary C-peptide levels in all three patients, with generally higher values during the day, when all were receiving three meals and three snacks, than during the overnight fasting periods.

In the second group, we found that measurement of urinary C-peptide excretion may be useful in assessing the role of endogenous insulin production as a determinant of insulin requirements. In the patients studied, urinary C-peptide levels in or near the normal range were related to low exogenous insulin requirements. Patients with low or negligible urinary C-peptide excretion had higher insulin requirements. However, patient 5, who had had diabetes for three years, had negligible urinary C-peptide excretion yet required relatively little exogenous insulin. He differed from the other subjects with diabetes of long duration and evidence of little or no endogenous insulin production in that he had a low level of insulin-binding antibodies. Thus, both insulin-binding antibodies and endogenous insulin appear to influence the dose of insulin required to maintain good diabetic control.

Endogenous insulin production has been postulated to influence exogenous insulin requirements and metabolic stability of juvenile diabetic patients.[2,3,17] It has been further proposed that measurement of serum C-peptide levels may aid in the management of juvenile diabetics.[18] Measurement of urinary C-peptide may be even more useful since urine collections can be done in patients' homes. For example, a patient complaining of frequent hypoglycemic episodes may have substantial endogenous insulin production and be receiving an excessive dose of exogenous insulin. Endogenous insulin production could be estimated over a 24-hour period or during the times of the hypoglycemic episodes by measurement of urinary C-peptide excretion.

Glycosylated hemoglobin determinations were used to substantiate the selection of patients for good diabetic control.[12,19] Seven of nine patients had glycosylated hemoglobin values below the mean value for patients judged to be in fair to poor control, 15.2% ± 1.5%. In addition, the selected patients' glycosylated hemoglobin values were less than the published means for juvenile diabetics of 12%[11] and 13.2%.[12] Some patients judged clinically to have been in good control and found to have minimal glucose spill had glycosylated hemoglobin levels of 8%, within 2 SDs of the mean for normal subjects. Good diabetic control was achievable in children both with and without substantial endogenous insulin production.

Recent studies[20-22] suggest that hyperglycemia results in exhaustion of β-cell secretion, further impairing glucose metabolism. Some have hypothesized that prompt, vigorous therapy of diabetic ketoacidosis as well as strict glucose control can enhance β-cell function and promote at least transient remission of diabetes.[5,23] It is possible that diabetic ketoacidosis per se suppresses insulin secretion and that correction of this metabolic derangement allows recovery of β-cell

function, a hypothesis compatible with the data from the three patients with ketoacidosis.

Measurement of urinary C-peptide excretion is a reliable index of β-cell function. Collections over short periods provide valuable data on short-term changes in insulin secretion. Since urine collections are easy to obtain in or out of the hospital, measurement of urine C-peptide excretion is an ideal method for longitudinal studies of β-cell function in diabetic patients. Such studies may also facilitate evaluation of newly available portable devices for continuous insulin delivery.[24-27]

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The nursing staffs of stations 32 and 56 of the University of Minnesota Hospitals, as well as the nursing and laboratory staffs of the Minneapolis Children's Hospital, assisted in studies of diabetic patients. Nancy Boyum also assisted in organizing and conducting this study. Mary Stahlmann, Carole Pesek, and Lois Schorle provided technical assistance. Roxanne Esslinger provided editorial assistance and, with Edith Cusher, provided secretarial assistance. David R. Brown, MD, Frederick C. Goetz, MD, and David M. Brown, MD, referred patients to this study.

References

1. Block MB, Rosenfield RL, Mako ME, et al: Sequential changes in β-cell function in insulin-treated diabetic patients assessed by C-peptide immunoreactivity. *N Engl J Med* 288:1144-1148, 1973.

2. Faber OK, Binder C: β-Cell function and blood glucose control in insulin-dependent diabetics within the first month of insulin treatment. *Diabetologia* 13:263-268, 1977.

3. Grajwer LA, Pildes RS, Horwitz DL, et al: Control of juvenile diabetes mellitus and its relationship to endogenous insulin secretion as measured by C-peptide immunoreactivity. *J Pediatr* 90:42-48, 1977.

4. Heding LG, Rasmussen SM: Human C-peptide in normal and diabetic subjects. *Diabetologia* 11:201-206, 1975.

5. Ludvigsson J, Heding LG: C-peptide in children with juvenile diabetes: A preliminary report. *Diabetologia* 12:627-630, 1976.

6. Ludvigsson J, Heding LG, Larsson Y, et al: C-peptide in juvenile diabetics beyond the postinitial remission period. *Acta Paediatr Scand* 66:177-184, 1977.

7. Madsbad S, Faber OK, Binder C, et al: Prevalence of residual β-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. *Diabetes* 27:262-264, 1978.

8. Horwitz DL, Rubenstein AH, Katz AI: Quantitation of human pancreatic β-cell function by immunoassay of C-peptide in urine. *Diabetes* 26:30-35, 1977.

9. Horwitz DL, Rubenstein AH, Mako ME, et al: C-peptide in conditions other than diabetes mellitus. *Diabetes* 27:267-271, 1978.

10. Fabiny DL, Ertingshausen G: Automated reaction rate method for determination of creatinine with the centrifichem. *Clin Chem* 17:696-700, 1971.

11. Trivelli LA, Ranney HM, Lai HT: Hemoglobin components in patients with diabetes mellitus. *N Engl J Med* 284:353-357, 1971.

12. Gabbay KG, Hasty K, Breslow JL, et al: Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. *J Clin Endocrinol Metab* 44:859-864, 1977.

13. Nakagawa S, Nakayama H, Saski T, et al: A simple method for the determination of serum free insulin levels in insulin treated patients. *Diabetes* 22:590-600, 1973.

14. Belmonte MM, Sarkozy E, Harpur ER: Urine sugar determination by the two-drop Clinitest method. *Diabetes* 16:557-559, 1967.

15. Morgan CR, Lazarow A: Immunoassay of insulin: Two antibody system. *Diabetes* 12:115-126, 1963.

16. Papadopoulou ZL, Tina LU, Sandler P, et al: Size and function of the kidneys, in Johnson TR, Moore WM, Jeffries JE (eds): *Children Are Different: Developmental Physiology.* Columbus, Ohio, Ross Laboratories, 1978, p 99.

17. Jackson RL, Guthrie RA: The child with diabetes. *Mo Med* 69:351-358, 1972.

18. Kuzuya H, Horwitz DL, Stelling M, et al: Blood sugar control in insulin requiring diabetics: Relationship of exogenous and endogenous insulin, abstracted. *Clin Res* 22:618A, 1974.

19. Jackson RL, Hewett JE, Hess RL, et al: Objective criteria for classifying degree of control in children with insulin dependent diabetes, abstract No. 54. *Diabetes* 27:444, 1978.

20. Turner RC, McCarthy ST, Holman RR, et al: β-Cell function improved by supplementing basal insulin secretion in mild diabetes. *Br Med J* 1:1252-1254, 1976.

21. Mirouze J, Selam JL, Pham TC, et al: Sustained insulin-induced remissions of juvenile diabetes by means of an external artificial pancreas. *Diabetologia* 14:223-227, 1978.

22. Genuth SM: Insulin secretion in obesity and diabetes: An illustrative case. *Ann Intern Med* 87:714-716, 1977.

23. Jackson RL, Murthy DYN: Importance of early insulin treatment and good regulation of children with diabetes. *Mo Med* 71:173-176, 1974.

24. New insulin-delivery systems for diabetics, editorial. *Lancet* 1:1275-1277, 1979.

25. Pickup JC, Keen H, Parsons JA, et al: Continuous subcutaneous insulin infusion: Improved blood-glucose and intermediary-metabolite control in diabetics. *Lancet* 1:1255-1257, 1979.

26. Tamborlane WV, Sherwin RS, Genel M, et al: Restoration of normal lipid and aminoacid metabolism in diabetic patients treated with a portable insulin-infusion pump. *Lancet* 1:1258-1261, 1979.

27. Deckert T, Lørup B: Regulation of brittle diabetics by a preplanned insulin infusion programme. *Diabetologia* 12:573-579, 1976.

Acute Pulmonary Exacerbations in Cystic Fibrosis

A Double-blind Trial of Tobramycin and Placebo Therapy

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• To determine the effect of antimicrobial therapy on acute pulmonary exacerbations in cystic fibrosis, a randomized, double-blind trial of tobramycin and placebo was carried out. Clinical responses were satisfactory in all 11 children given tobramycin and in seven of 11 given placebo. Two patients in the placebo group died. No patient given placebo had improved results on pulmonary function studies, whereas improvement of 15% or more occurred in four of the six patients given tobramycin who could cooperate with the testing. Quantitative cultures of sputum showed a decrease of 1 logarithm or greater in *Pseudomonas* sp concentrations in six of seven patients in the tobramycin group and in two of eight in the placebo group. No difference in staphylococcal colonization was found. Several features indicate that children with severer disease were randomly assigned to the placebo group; nevertheless, the trend toward improved response in patients given tobramycin suggests that empirical therapy with antibiotics is beneficial for patients with acute pulmonary exacerbations in cystic fibrosis.

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Gram-negative bacilli, chiefly *Pseudomonas* sp, and *Staphylococcus aureus* frequently infect the lower respiratory tracts of patients with cystic fibrosis (CF). For several reasons, the role these organisms play during acute exacerbations of pulmonary disease is equivocal. They are as likely to be present during asymptomatic intervals as during periods of pulmonary deterioration. Antimicrobial therapy during periods of pulmonary exacerbation rarely eradicates the organisms from the tracheobronchial tree, and eradication is not necessary for regression of pulmonary symptoms. Systemic infection with these potential pathogens is rare, even in the most debilitated patients. The improved longevity that patients with CF now experience is possibly due as much to scrupulous attention to pulmonary toilet and nutrition as it is to the use of antibiotics. Finally, to our knowledge, no controlled studies have been performed to evaluate the role of therapy with antibiotics in acute pulmonary exacerbations of CF.

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Reprints not available.

MATERIALS AND METHODS

Patient Populations

Between April 1976 and June 1977, pediatric patients admitted to Children's Medical Center, Dallas, because of acute pulmonary exacerbation of CF were included in the study after informed parental consent was obtained. Patients were excluded from study if they were judged to have life-threatening illness or had empyema, pneumothorax, liver failure, or systemic infection. In addition, patients were removed from the study if bronchoscopy or bronchial lavage was required during hospitalization.

Therapy

On admission to the study, patients were assigned by a list of random numbers to receive either tobramycin or placebo. Tobramycin, 2 mg/kg, was given every eight hours as a one-hour continuous infusion. The placebo was a lactose solution prepared by Lilly Research Laboratories, which was administered in an identical fashion. Therapy was continued daily until the time of discharge from the hospital or until persistence or worsening of symptoms required breaking the code.

In addition to placebo or tobramycin, all patients admitted to the study received intensive chest physiotherapy administered in a standard fashion four times a day. Parenteral and oral hydration therapy, bronchodilators, and oxygen were given when needed.

Pharmacokinetic Evaluation

Pharmacokinetic evaluation of most of the patients given tobramycin was performed on the third hospital day. Blood for the tobramycin assay was collected one and six hours after the one-hour infusion of the drug. Serum was separated and frozen at −70 °C until the assay was performed. Concentrations of tobramycin in serum were measured by the micromethod of Simon and Yin,[1] using *Bacillus subtilis* as the test organism. Sputum specimens for tobramycin assay were collected one and eight hours after the dose. A homogenized mixture of sputum and 2% *N*-acetyl-L-cysteine (NAC) was prepared in a ratio of 1 mL of NAC to 1 g of sputum, centrifuged at 4 °C for 20 minutes at 12,000 rpm, and the supernatant assayed for tobramycin concentration. This concentration of NAC did not affect the assay organism. Known concentrations of tobramycin added to sputum of patients with CF who were not receiving antibiotics were simultaneously assayed as control specimens. Sputum was collected from study patients before administration of the first dose of tobra-

mycin and assayed for the presence of inherent antibacterial activity, and this amount was subtracted from the tobramycin assay.

Bacteriologic Studies

Quantitative cultures of sputum were obtained from patients old enough to provide expectorated specimens. This was done after 15 minutes of intensive chest physiotherapy before the first dose of tobramycin or placebo and then at four- to six-day intervals. Sputum for bacterial measurement was frozen at −20 °C for two minutes and carefully separated from saliva. One gram of frozen sputum was liquified by the addition of 1 mL of a 2% solution of NAC and homogenized for one minute at 9,000 rpm in an agitator. Serial tenfold dilutions of this homogenate were prepared in brain-heart infusion broth and plated in duplicate on 5% sheep blood agar and eosin-methylene blue agar plates. Identification of organisms was by standard bacteriologic methods. Results were expressed as the number of colony-forming units (CFU) per gram of sputum.

Strains of *Pseudomonas* and *S aureus* isolated from cultures of sputum were tested for tobramycin sensitivity by Mueller Hinton agar plate dilution, using a bacterial inoculum of 10^4 CFU/mL.

Clinical Evaluation

Clinical evaluation was carried out by one of two physicians (R.I.K., C.W.P.) who were unaware of the patient's parenteral therapy. Twice-daily review of the patients' progress included noting the general level of activity, appetite, personality, disposition, a description of the amount, thickness, and ease of production of sputum, and the Schwachman score. In addition, the patients' weight, body temperature, oxygen requirements, and resting pulse and respiratory rates were recorded. Chest roentgenograms were performed at the times of admission to the study and discharge, and were interpreted by a radiologist who had no knowledge of the patients' treatment. Vital capacity (VC), peak expiratory flow rates (PEFR), and forced expiratory volume at 1 s (FEV_1) were evaluated at the time of admission to the study and at five-day intervals in children old enough to comply with the techniques. There is a reproducibility error of 5% to 10% with these tests; therefore, a change of 15% or more with time was considered significant.

Statistical Analysis of Data

Student's t test and Fisher's exact test were used to test for differences between the two treatment groups in patient characteristics such as age, sex, roentgenographic pulmonary changes, etc. The z test with two proportions[2] was used to test for differences between the groups in clinical and laboratory responses to therapy.

RESULTS

Patient Characteristics

Twenty-two patients were admitted to the study and received 24 courses of therapy, 12 each of tobramycin and placebo. Two patients were admitted to study on two separate occasions after intervals of three or four months and received, by random assignment, therapy that was different from the initial treatment.

Table 1 gives the pertinent characteristics of the two treatment groups. Patients given placebo tended to be younger, to have more severe roentgenographic pulmonary changes, to have greater reversal of the normal albumin-globulin ratio, and to require more hospitalizations for pulmonary infection, and were more likely to be free of colonization with *S aureus* than were the patients given tobramycin. None of these differences was statistically significant, although the difference between the two groups in number of hospitalizations ($P > .5$) and prevalence of *S aureus* ($P = .11$) approached significance.

Mean initial colony counts of 1.2×10^8 CFU of *Pseudomonas* sp per gram of sputum in the placebo group exceeded by almost 2 logarithms the mean initial counts found in the tobramycin group. Conversely, the mean initial number of CFU of *S aureus* in the placebo group was 2 logarithms lower than those found in the tobramycin group (2.2×10^6 vs 2.2×10^8 CFU/g of sputum).

Clinical Response

The clinical responses to therapy are given in Table 2. Two children, one in each group, could not be evaluated. One was withdrawn from the study after three days of therapy with placebo at the parents' request and one completed five days of therapy with tobramycin, but inadequate clinical data were recorded. All of 11 patients given tobramycin had satisfactory clinical responses, whereas only seven of the 11 placebo-group patients had a comparable response. Deterioration of

Table 1.—Comparison of Study Groups

Characteristics	Placebo Therapy	Tobramycin Therapy
No. of courses	12	12
Age		
Mean	8.5 yr	10.5 yr
Range	3-16 yr	9 mo-27 yr
Sex, M:F	6:6	7:5
% of predicted weight for age		
Mean	67	68
Range	45-96	41-91
Roentgenographic pulmonary changes, No. of patients		
Severe	9	6
Moderate	2	2
Mild	1	4
Serum albumin-globulin ratio		
Mean	1.6	1.2
Range	0.75-3.2	0.8-1.9
No. of hospital admissions for pulmonary infection		
Mean	4.7	3.1
Range	2-8	1-10
Initial sputum culture, No. of patients		
Mucoid *Pseudomonas*	11	10
Staphylococcus aureus, *Pseudomonas*	3	8
Initial quantitative bacteriology*		
Pseudomonas	1.2×10^8	1.5×10^8
Staphylococcus aureus	2.2×10^6	2.2×10^8

*Mean number of colony-forming units per gram of sputum.

Table 2.—Clinical Response to Therapy

Outcome of Therapy	Placebo, 12 Patients	Tobramycin, 12 Patients
Satisfactory	7	11
Unsatisfactory	4	0
Died	2	0
Unevaluable	1	1

the clinical status required the removal from the protocol of three children given placebo. Two of these were subsequently given antibiotics and had satisfactory clinical outcomes. The third patient was removed from study after two days of therapy with placebo and subsequently died after two days of treatment with gentamicin sulfate. The fourth patient with unsatisfactory outcome died after 24 hours of therapy with placebo. The difference in outcome between the two treatment groups borders on statistical significance ($P > .5$) (z test with two proportions).

Laboratory Findings

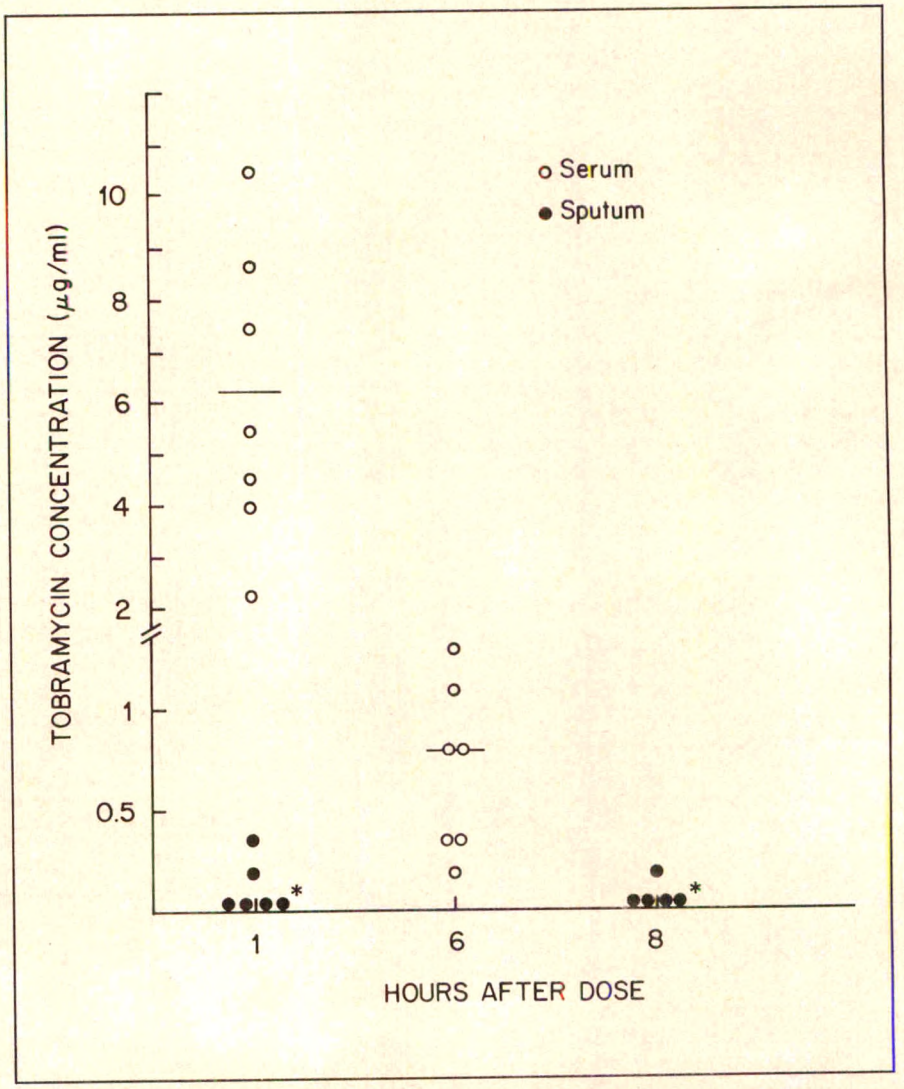
Table 3 gives the pertinent respiratory and bacteriologic responses to therapy in the two groups. No patient given placebo demonstrated improvement in pulmonary function studies, whereas four of six children given tobramycin showed 15% or greater improvement in at least two of the three tests performed (VC, FEV_1, PEFR). This difference in pulmonary function was statistically significant ($P < .05$) (z test). Chest roentgenograms showed no consistent changes in most patients in either group during the course of treatment with placebo or tobramycin.

In patients given placebo, the bacterial concentrations in sputum ranged from 4.6×10^6 to 9.5×10^8 CFU/g of sputum for *Pseudomonas* sp and from 9.1×10^4 to 5.8×10^6 CFU/g for *S aureus*. The range of bacterial counts for the tobramycin group was from less than 10^2 to 4.4×10^6 for *Pseudomonas* sp and from 9.6×10^5 to 1.7×10^9 for *S aureus*. Tobramycin treatment was associated with a 1 logarithm or greater decrement in *Pseudomonas* sp concentrations in sputum of six of seven patients, although this occurred in only two of

Table 3.—Laboratory Features of Response to Therapy

	Placebo, No. of Subjects	Tobramycin, No. of Subjects
Pulmonary function studies*		
Improved	0/7	4/6
Worsened	1/7	0/6
Chest roentgenogram		
Improved	3/9	1/9
Worsened	1/9	1/9
Quantitative bacteriology of sputum		
Pseudomonas		
≥ 1 logarithm decrease	2/8	6/7
≥ 2 logarithm decrease	1/8	3/7
≥ 1 logarithm increase	1/8	0/7
Eradication	0/8	1/8
Staphylococcus aureus, 1 logarithm decrease	2/3	2/7

*Consistent change of at least ±15% in two of three tests (vital capacity, peak expiratory flow rates, and forced expiratory volume at 1 s).



Concentrations of tobramycin in serum and sputum from seven patients. Specimens indicated with asterisk were below lower limit of sensitivity of assay (0.2 μg/g).

eight patients given placebo. The one patient in the tobramycin group who did not show a significant decrease in *Pseudomonas* concentration had colony counts of 3.6×10^5 on day 1 of therapy and 4.4×10^4 on day 10. The changes in *Pseudomonas* colony counts for the two therapy groups was of borderline significance ($P > .5$). There were no differences between the two groups with respect to the changes in colony counts of *S aureus*.

The Figure presents the concentrations of tobramycin in sputum and serum. The mean serum tobramycin concentrations at one and six hours after the dose were 6.2 and 0.7 μg/mL, respectively. These concentrations exceeded the mean minimal inhibitory concentrations (MIC) of 0.46 and 0.24 μg/mL for five strains of *S aureus* and nine strains of *Pseudomonas* sp, respectively, obtained from study patients. Isolates of *Pseudomonas* sp and *S aureus* obtained on days 5 or 10 of therapy remained susceptible to tobramycin. Concentrations of tobramycin in sputum at one and eight hours after intravenous (IV) administration of the drug were less than the lower limit of the assay (0.2 μg/g) for four of six peak and four of five trough specimens. Concentrations of 0.3 to 0.2 μg/g were achieved in sputum of three patients.

Nephrotoxicity was not encountered in the patients given tobramycin.

COMMENT

The outcome of acute pulmonary exacerbations of CF reflects many independent variables that operate simultaneously: the waning with time of intercurrent viral infection,[3] hydration and nutritional support, aggressive chest physiotherapy and postural drainage,[4] and antimicrobial therapy. Our study attempted to evaluate the contribution of this last variable. The clinical response to therapy with tobramycin tended to be favorable when compared with treatment with placebo, but this difference was only of borderline statistical significance. This trend is supported by the significant improvement in the tobramycin group in sequential pulmonary function studies and by the greater reduction in sputum colony counts of *Pseudomonas* sp. In addition, two patients initially given placebo died after one and four days of hospitalization. Although it is possible that antimicrobial therapy may not have prevented either death, these early adverse outcomes occurred in a study in which the participants were observed closely and that excluded patients judged by experienced physicians to have life-threatening pulmonary exacerbations.

Most published studies of therapy with antibiotics for CF,[5-7] although suggesting clinical benefits to its use, have failed to include control groups for analysis, even after the skepticism voiced almost a decade ago.[8] Consequently, there are few studies of CF that resemble the present work closely enough in design to allow comparisons. A double-blind trial of therapy with continuous oral cloxacillin sodium or placebo given on an ambulatory basis for 12 months to 22 patients with CF was carried out by Denning et al.[9] Statistical analysis of results is not reported, but there was less progression of pulmonary disease as evaluated by chest roentgenograms, pulmonary function studies, and blood gas determinations in the group given antibiotics. Similar beneficial effects of long-term therapy with antibiotics for patients with CF have been reported by Loening-Baucke and coworkers,[10] who demonstrated improved weight gain and significant decrease in the number and severity of respiratory illnesses for patients infected with *S aureus* and treated with cephalexin monohydrate. Although suggesting a role for continuous therapy with antibiotics in the suppression of the chronic bronchitis of the ambulatory patient with CF, these studies do not address the question of the efficacy of antimicrobial therapy for acute pulmonary exacerbation in the hospitalized patient.

In a randomized but nonblind study, Beaudry and co-workers[11] compared the effectiveness of therapy with parenteral cloxacillin alone or with carbenicillin plus gentamicin for acute pulmonary flare-ups in 22 patients with CF. Children in both treatment groups had *P aeruginosa* as the predominant respiratory flora. No difference was found between clinical outcomes of the two groups, which led the authors to question the justification of anti-*Pseudomonas* therapy.

If antimicrobial therapy had a beneficial influence on the bacteriologic course of disease in our patients, efficacy was not a function of tobramycin levels in sputum. In only three of 12 determinations were detectable amounts of tobramycin found, and two of these three had amounts below the mean MIC for both the staphylococcal and *Pseudomonas* isolates tested. Penetration of tobramycin into bronchial secretions has been studied in other experimental settings, with results different from ours. In the dog, mean peak tobramycin concentrations in bronchial secretions of 1.15 μg/mL were detected two hours after IV administration.[12] In adult patients without CF, the mean tobramycin concentration of 3.75 μg/mL in bronchial secretions approached 67% of the concomitant serum levels when calculations were based on bronchial secretion standards.[13] However, when concentrations were calculated from the serum standards, the values were less than 1 μg/mL. The difference between the scant concentrations of tobramycin in sputum from our patients and the considerably higher levels reported by others may be due to a variety of factors. These include the type of standard curve used in calculations, the method of collection of the secretion (bronchoscopy and intubation vs expectoration), and the much larger volume of bronchial secretions produced by infected patients with CF that acts to dilute the amount of tobramycin reaching the airways. In a small group of patients with CF, McCrae et al[7] found a mean tobramycin level in sputum of 0.4 μg/mL after a parenteral dose of 2 mg/kg. In that study, which used a bioassay with *Pseudomonas* as the test organism, the method of sputum preparation was not outlined, nor is it certain that inherent anti-*Pseudomonas* activity of sputum was taken into account. For therapy for CF, high sputum concentrations of antibiotic may be an attractive artifact and not a necessary

condition for clinical and bacteriologic improvement, as was suggested by the present study. More important to effective therapy than concentration of antibiotic in sputum may be the concentration of antibiotic perfusing the bronchial mucosa.

Little effort has been devoted to the study of the quantitative bacteriology of the sputum of patients with CF. Mischler et al[14] reported bacterial counts of 10^6 to 10^8 CFU/mL of sputum for *S aureus* and 10^4 to 10^8 CFU/mL for *P aeruginosa* in nine patients with CF who had acute pulmonary exacerbations; these levels are similar to those found in our study. These investigators[14] documented significant reduction in the concentration of *S aureus* during therapy with antibiotics (type unspecified), but were unable to show a concomitant decrease in the concentration of *Pseudomonas*. By contrast, all but one of our patients given tobramycin had at least a 1-logarithm decrease in *Pseudomonas* colony counts, and in half of these decreases of 2 logarithms were found. Eradication of *Pseudomonas* was achieved in one patient. This was not the case with *S aureus*, where only two of seven patients who received tobramycin experienced greater than 1-logarithm decreases in colony counts.

Although strict statistical significance is lacking, the results of this study suggest that outcome of acute pulmonary exacerbation of CF is benefited by the use of antimicrobial therapy. However, this interpretation of the results of the present study is complicated by two factors. First, the relatively small number of patients in each treatment group makes statistical analysis difficult. Second, the placebo and tobramycin groups, though chosen randomly, were not strictly comparable. Several characteristics of the placebo group suggest that these patients may have had more advanced disease than did those in the tobramycin group.

Placebo-group patients harbored significantly greater numbers of *Pseudomonas* organisms in the tracheobronchial tree than did those in the tobramycin group, and fewer patients in the placebo group had concomitant staphylococcal colonization. Kulczycki et al[15] have recently suggested that exclusive, heavy *Pseudomonas* infection may correlate with greater severity of disease and worsened prognosis. Other characteristics of the placebo group that suggest more severe underlying disease include a greater number of prior hospitalizations for pulmonary problems, a greater likelihood of severe disease on chest film, and greater reversal of the albumin-globulin ratio.

It is possible, therefore, that the apparently favorable response to therapy with tobramycin may have reflected the natural history of the disease in the less severely affected patient, rather than the effects of antimicrobial therapy. Additional investigation may be needed to clarify this question. Until such new data are forthcoming, it is advisable to continue to use empirical antimicrobial therapy for respiratory exacerbations of CF.

Helen Kusmiesz, RN, assisted with collection of specimens and clinical records.

Nonproprietary Names and Trademarks of Drugs

Gentamicin sulfate—*Garamycin, Genoptic.*
Tobramycin—*Nebcina.*

References

1. Simon H, Yin J: Microbioassay of antimicrobial agents. *Appl Microbiol* 1970;19:573-579.
2. Rimm AA, Hartz AJ, Kalbfleisch JH, et al: *Basic Biostatistics in Medicine and Epidemiology.* New York, Appleton-Century-Crofts, 1980.
3. DeForest A, Groz HG, Laraya-Causay LR, et al: A serologic study of *Mycoplasma pneumoniae* and respiratory syncytial virus infections in patients with cystic fibrosis, in *Cystic Fibrosis Club Abstracts.* Atlanta, Cystic Fibrosis Foundations, 1976, p 31.
4. Wood RE, Bota TF, Doershik CF: Cystic fibrosis. *Am Rev Respir Dis* 1976;113:833-878.
5. Hoff GE, Schiotz PO, Paulsen J: Tobramycin treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis. *Scand J Infect Dis* 1974;6:333-337.
6. Hawley HB, Lewis RM, Swartz DR, et al: Tobramycin therapy of pulmonary infections in patients with cystic fibrosis. *Curr Ther Respir* 1974;16:414.
7. McCrae WM, Raeburn JA, Hanson EJ: Tobramycin therapy of infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis: Effect of dosage and concentration of antibiotic in sputum. *J Infect Dis* 1976;134 (suppl):191-193.
8. Marks MI, Prentice R, Sivarson R, et al: Carbenicillin and gentamicin: Pharmacologic studies in patients with cystic fibrosis and *Pseudomonas* pulmonary infections. *J Pediatr* 1971; 79:822-828.
9. Denning CR, Park S, Grece CA, et al: Continuous vs intermittent oral antibiotics in the management of patients with cystic fibrosis, in *Cystic Fibrosis Club Abstracts.* Atlanta, Cystic Fibrosis Foundation, 1977, p 13.
10. Loening-Baucke VA, Mischler E, Myers MG: A placebo-controlled trial of cephalexin therapy in the ambulatory management of patients with cystic fibrosis. *J Pediatr* 1979;95:630-637.
11. Beaudry PA, Marks MI, McDougall D, et al: Is anti-*Pseudomonas* therapy warranted in acute respiratory exacerbations in children with cystic fibrosis? *J Pediatr* 1980;97:144-147.
12. Pennington JE, Reynolds HY: Tobramycin in bronchial secretions. *Antimicrob Agents Chemother* 1973;4:299-301.
13. Alexander MR, Berglund EM, Kasik JE: The concentration of tobramycin in bronchial secretions. *Chest* 1979; 75:675-678.
14. Mischler EH, Younoszai MR, Myers MG: Quantitative sputum cultures in hospitalized patients with cystic fibrosis, in *Cystic Fibrosis Club Abstracts.* Atlanta, Cystic Fibrosis Foundation, 1976, p 50.
15. Kulczycki LL, Murphy TM, Bellanti JA: Pseudomonas colonization in cystic fibrosis. *JAMA* 1978;240:30-34.

Menarchal Determinants in Cystic Fibrosis

Thomas Moshang, MD, Douglas S. Holsclaw, Jr, MD

• Age, derived fat index (FI), and clinical score at the time of menarche were determined from records of 63 girls with cystic fibrosis (CF) and from 17 comparably aged but nonmenarchal girls with CF. The mean age of menarche in girls with CF was 14.5 years at a mean FI of 20.1% fat; thus, they were significantly older and had less fat than normal girls. Menarchal age was related to severity of illness. Amenorrheic girls with CF, mean age of 14 years, were significantly sicker and smaller. Gonadotropin and estradiol levels in 23 girls with CF were normal. The delay in menarche in CF appears to be closely related to severity of illness. Furthermore, although the relationship of puberty to body composition may or may not be coincidental, it is unlikely that puberty is initiated by a "critical body composition."

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Data from the Cystic Fibrosis Foundation Registry indicate that the majority of patients with cystic fibrosis (CF) will survive their teen years.[1] Not surprisingly, a major concern of this enlarging population of adolescents relates to their sexual development. Delay in sexual development is recognized as a significant, although not universal, complication of CF.[2,3] The study of factors involved in the sexual maturation of patients with CF may provide information useful not only for therapeutic benefits and emotional relief for patients by allowing for anticipatory counseling but also may provide further insight into some of the physiologic factors controlling the onset of puberty.

Puberty obviously is a complex maturational process involving changes in secretions of neuroendocrine and gonadal hormones. The factors responsible for initiating changes in hormonal secretions and onset of puberty in human beings are still obscure. The hypotheses that pubertal events are secondary to maturational or time-dependent changes in the hypothalamus[4,5] do not explain the increased incidence of delay in sexual development in a number of illnesses, such as malnutrition, diabetes mellitus, and CF. Frisch and associates have proposed that the initiation of puberty is "triggered" by the attainment of a critical body composition, ie, a specific increase in fat in relation to lean body mass alters the metabolism of gonadal steroids, which in turn initiates the onset of development of secondary sexual characteristics.[6-8] Our present study of menarchal determinants in girls with CF supports the findings of Frisch and associates that menarche can be delayed by the lack of attainment of a critical body composition but also suggests that other factors are more directly responsible for initiation of puberty.

METHODS

Records of all female patients, both living and dead, registered at two regional CF centers were reviewed. Only those records that clearly documented the first menstrual period or clearly indicated the continued absence of menarche were used. For 63 menarchal girls with CF, the height, weight, and clinical assessment (clinical score) of severity of disease[9] noted at the visit most proximate (< three months) to the menarchal event were obtained. Similar data were abstracted from the most recent clinic visit of 17 girls with CF who were older than 12.5 years and still amenorrheic. Menarchal age and weight were obtained by history for the patients' sisters and mothers (not affected by CF) and documented by written record when possible.

Body composition (total body water [TBW] as a percentage of body weight [BW] and body fat [BF] as a percentage of BW) was derived from weight (kilograms) and height (centimeters) measurements with the following formulas[10-12]:

$$TBW = (-10.313 + 0.252\,[\text{weight}]) + 0.0154\,(\text{height})$$

$$\text{Lean body mass} = TBW/72$$

$$BF = BW - \text{lean body mass}$$

Since the components of body composition are reciprocally related, an increase in

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Clinical Data and Derived Body Composition						
Patients*	Age, yr	Height, cm	Weight, kg	% Body Water	% Body Fat	Clinical Score
Normal subjects (181)	12.9±1.2†	158.5±6.7	47.8±6.8	55.1±3.6	23.5±4.8	. . .
Menarchal with CF (63)	14.5±1.6	156.4±7.2	43.8±6.8	57.3±4.0	20.1±4.0	74.2±14.2
Amenorrheic with CF (17)	14.0±1.3	151.2±8.5	35.0±7.7	63.2±5.7	11.7±8.3	40.0±29.5
Statistical Analysis‡						
Normal vs menarchal	$P < .001$	$P < .05$	$P < .01$	$P < .02$	$P < .02$	. . .
Menarchal vs amenorrheic	NS	$P < .01$	$P < .001$	$P < .001$	$P < .001$	$P < .001$

*Normative data from published results of Frisch et al.[7] CF indicates cystic fibrosis.
†Mean ± SD.
‡Statistical analysis using Student's *t* test.

the percent TBW must be accompanied by a corresponding decrease in the percent BF. For the remainder of this study, body composition will refer to the percent BF, called the "fat index."

Although these formulas were derived from measurements obtained from normal children and adults and may not be accurate when applied to patients with CF, similar derivations have been used in studies of bedridden and ambulatory mentally retarded children[13] and in comparisons of children with various disorders of sexual development to normal children.[14]

Twenty-three cases of living female patients with CF, aged 10 to 18 years, were evaluated in terms of pubertal development with the method of Tanner[15] and were segregated into the following groups: (1) completely prepubertal; (2) early adolescence; (3) late adolescence; and (4) adults. Early adolescence was defined as patients with mainly Tanner's 2 or 3 staging in the various areas of secondary sexual development. Late adolescence was confined to those patients with menarche and/or Tanner's 3 and 4 staging in most of the areas of secondary sexual development.

Serum samples were obtained from these patients for determination of levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2). Serum LH and FSH levels were determined by a double-antibody radioimmunoassay technique with a commercial kit (Radioassay Systems); values were reported as International milliunits per milliliter (Second International Reference Standard of Human Menopausal Gonadotropin [standard provided by Dr Bingham of Mill Hill, England]). Serum E_2 levels were determined by a double-antibody radioimmunoassay.[16]

RESULTS

A comparison of the physical data for girls with CF and the data of Frisch et al[7] for normal girls is summarized in the Table. The mean age for menarche in the girls with CF was 14.5 years. This value is similar to the finding of 14.2 years reported by both Stern et al[2] and Mitchell-Heggs et al[17] and exceeds the mean menarchal age of the patients' mothers (13.0 years), the patients' sisters (13.1 years), and normal girls (12.9 years).[7] The patients with CF also achieved menarche at a shorter height, lower weight, and lower derived fat index as compared with normal girls. Although the mean value for fat index for the 63 menarchal girls with CF was 20.1%, 13 of the 62 (20%) achieved menarche at a body composition less than the proposed critical body composition of 17% body fat (59.8% TBW/BW)[8] (Fig 1). Two of the patients with CF achieved menarche at a fat index composition of only 7%.

The Table also compares the clinical score of the menarchal CF females with a group of amenorrheic girls with CF of similar age. The amenorrheic girls were significantly sicker (as indicated by the clinical score) and shorter and lighter. The mean body composition of the amenorrheic patients was 11.7% BF, significantly below the mean value of 20.1% BF of the menarchal CF group and significantly less than Frisch and McArthur's proposed "critical" 17% BF.[8]

The correlation of age of menarche to severity of illness is shown in Fig 2. The more severe the illness is (lower clinical score) the more delayed is the onset of menarche ($r = -.43$, $n = 63$, $P < .01$).

The serum values for LH, FSH, and

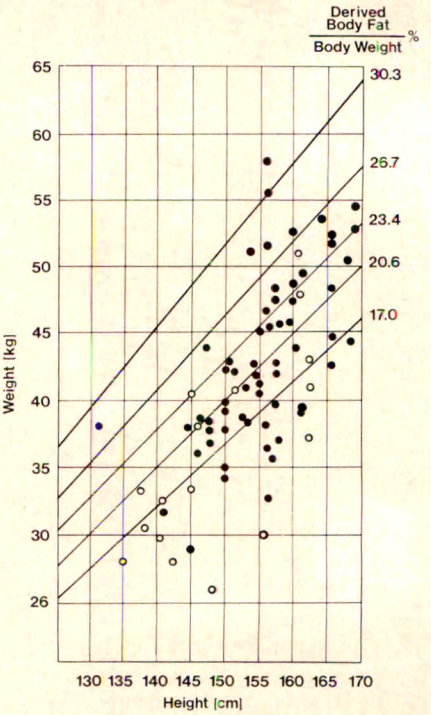


Fig 1.—Height and weight of menarchal patients with cystic fibrosis (CF) (solid circles) and primary amenorrheic patients with CF (open circles) are plotted on modification of graph designed by Frisch and McArthur.[8] Proposed minimal body fat content necessary for menarche is 17%.

E_2 were generally lower than the mean value for chronologic age for normal girls but were within the normal range (Fig 3). When the hormone values of girls with CF were plotted according to stage of pubertal development, FSH and E_2 values were comparable to values found in normal girls at corresponding stages. The LH values, however, remained in the lower ranges of normal, except in patients in group 4 (Fig 3). In general, the gonadotropin and E_2 levels for patients with CF are considered to be within the normal range.

COMMENT

Those factors primarily responsible for initiating puberty in human beings are still not fully defined. Frisch and her associates have hypothesized that body composition is an important determinant for the onset of puberty.[6-8] Other investigators have suggested that the changes in body composition during puberty are coincidental and secondary to gonadal hormone activity.[18] By excluding any

relationship of body composition to initiation of pubertal events, this viewpoint does not explain the decrease in gonadotropin levels or delay in development of secondary sexual characteristics during states of malnutrition or other illnesses.

In our study, patients with CF who were still amenorrheic despite having attained a fairly advanced chronologic age had advanced pulmonary disease and malnutrition. They had a mean body composition in which the derived fat index of 11.7% was significantly less than the minimally necessary 17% BF as proposed by Frisch and McArthur.[8] Although several of the amenorrheic patients with CF had body compositions with fat indices greater than 17%, Frisch has indicated that this proposed critical body composition is the minimal percent BF to be achieved before menarche ensues and that menarche can occur at greater fat indices. Our observations of the marked delay of menarche in CF, when correlated with the body composition data, would, at first analysis, tend to support the "Frisch" hypothesis.

However, the basis of the original hypothesis of Frisch et al[6,7] was the finding of an "invariant mean weight" at menarche in different populations of menarchal girls, including undernourished patients. Critics of this hypothesis included Johnson et al,[19] who noted that mean weight at menarche was not invariant among several different populations. The girls with CF achieved menarche at a mean weight of 43.8 kg, significantly less than normal girls. Frisch and McArthur[8] subsequently modified the hypothesis and proposed that puberty was initiated by attainment of a "critical" body composition, with the use of both height and weight to derive TBW and BF.

Nevertheless, using the same formulas to derive TBW and BF, we found the mean percent BF at menarche in CF to be 21.1%, significantly less than that in the normal girls. In fact, the distribution of individual body composition at menarche was shifted downward, so that only 17 of the 63 patients (20%) exceeded the mean value for percent BF of normal

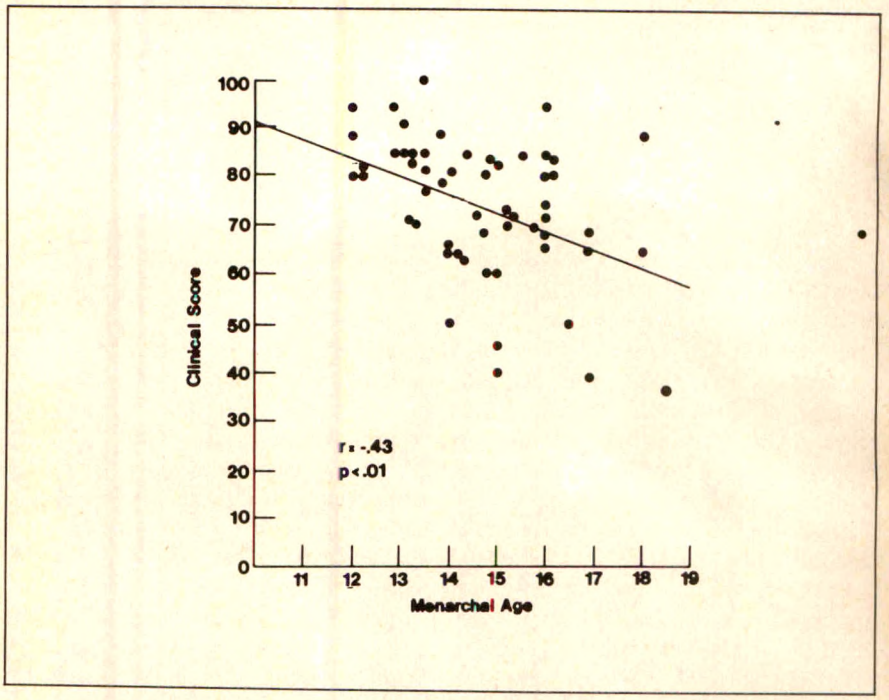
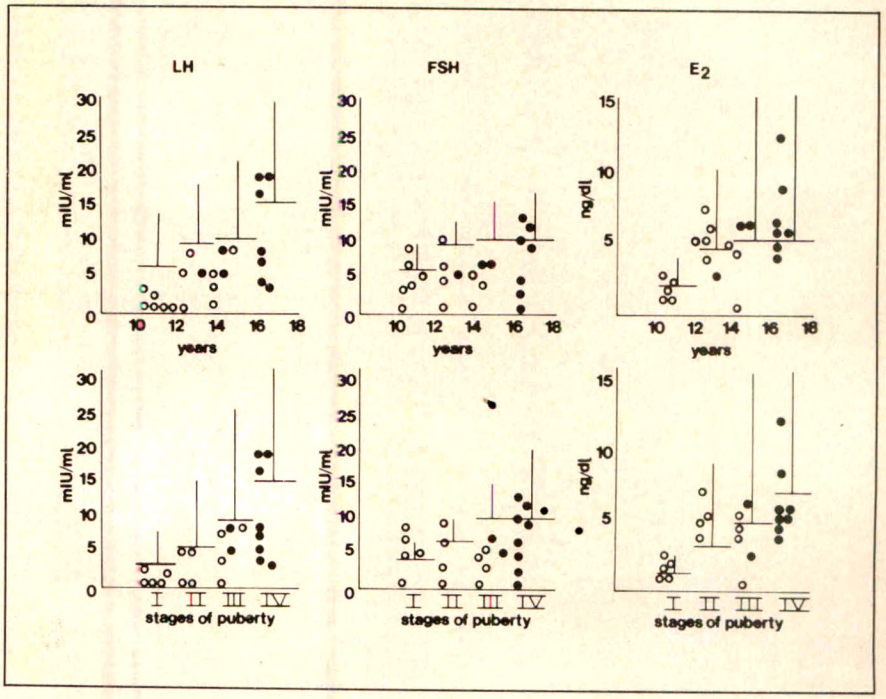


Fig 2.—Correlation of age of menarche to clinical score of patient at time of menarche in patients with cystic fibrosis.

Fig 3.—Serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) for 23 adolescent girls with cystic fibrosis (solid circles represent menarchal patients; open circles represent patients who are still amenorrheic) are plotted against age and sexual maturation. Mean value for normal girls in our laboratory is represented by horizontal bar. Perpendicular line represents normal values 2 SDs greater than mean.



girls and 20% achieved menarche with much less BF than the proposed critical 17%. Two of these latter patients achieved menarche with a derived fat index of 7% BF (and at older ages: 16.5 and 17.3 years). Although the findings in the amenorrheic girls with CF suggest that lack of attainment of a critical body composition may delay menarche, the body composition data of the menarchal girls indicate that other factors will eventually initiate puberty. In fact, the significant percentage of girls with CF achieving menarche at fat indices less than the proposed critical level would indicate that the primary factors responsible for initiating puberty are not fat content or body composition and that these factors can overcome in time any feedback control sensitive to inanition or body composition.

The Mellits-Cheek formulas used by Frisch and her associates and by us to calculate lean body mass, TBW, and BF were derived from studies in normal children. The use of these formulas in the studies of Frisch and associates has been criticized because of their inaccuracies, especially when applied to "abnormal" children, such as the undernourished children in the Alabama study.[20] Similarly, the possible inaccuracies of these formulas when applied to children with CF must be acknowledged. Forbes et al, with the use of ^{40}K counting, has noted that BF was subnormal in 50% of patients with CF.[21] Obviously, prospective studies relating body composition to puberty should use more accurate methods.

The gonadotropin and E_2 levels in our patients were within the range of values for normal girls, especially when correlated with sexual maturation. Serum LH levels, however, remained slightly lower than anticipated, except in the most physically mature girls with CF as compared with the normally distributed levels of FSH. Discordantly low LH values, as compared with FSH values, have been noted in anorexia nervosa.[22,23] The explanation for the low LH values in states of inanition is not known, although Warren[23] has suggested that the pituitary tropic cells for LH may be more sensitive to weight loss than the FSH gonadotroph. The normal serum levels of gonadotropins and estrogens in the more mature patients with CF, as well as the findings of Reiter and associates[24] of normal gonadotropin responses to gonadotropin-releasing hormone, indicate that there is no primary dysfunction in the hypothalamic-pituitary-gonadal axis in CF. The capability of a number of the girls with CF to become pregnant and carry their infants to term would also tend to substantiate this.

Our data suggest that the delay in pubertal development in girls with CF is closely related to the severity of their disease and nutritional status. The healthier female adolescents with CF can certainly be reassured of their eventual sexual maturation. Furthermore, our study suggests that the interrelationship between body composition and puberty may not be a coincidental relationship and that the neuroendocrine mechanisms controlling onset of puberty can be modified by various factors, including inadequate fat reserve. However, the significant percentage of girls with CF with low fat indices achieving menarche, albeit often very delayed, indicates that body composition is not the factor that directly initiates onset of puberty.

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References

1. *1977 Report on Survival Studies of Patients With Cystic Fibrosis.* Rockville, Md, Cystic Fibrosis Foundation, 1979, p 5.

2. Stern RC, Boat TF, Doershuk CF, et al: Course of cystic fibrosis in 95 patients. *J Pediatr* 89:406-411, 1976.

3. Moshang T, Holsclaw DS, Habboushe C, et al: Gonadotropins and sex steroids in adolescents with cystic fibrosis. *Cystic Fibrosis Club Abstracts* 17:16, 1976.

4. Kulin HE, Grumbach MM, Kaplan SL: Changing sensitivity of the pubertal gonadal hypothalamic feedback mechanism in man. *Science* 116:1012-1013, 1969.

5. Grumbach MM, Roth JC, Kaplan SL, et al: Hypothalamic-pituitary regulation of puberty in man: Evidence and concepts derived from clinical research, in Grumbach MM, Grave GD, Mayer FE: *The Control of the Onset of Puberty.* New York, John Wiley & Sons Inc, 1974, pp 115-116.

6. Frisch RE, Revelle R, Cook S: Height, weight and age at menarche and the 'critical weight' hypothesis. *Science* 174:1148-1149, 1971.

7. Frisch RE, Revelle R, Cook S: Components of the critical weight at menarche and the initiation of the adolescent spurt: Estimated total body water, lean body mass and fat. *Hum Biol* 45:469-483, 1973.

8. Frisch RE, McArthur JW: Menstrual cycles: Fatness as a determinant of minimum weight for height necessary for their maintenance or onset. *Science* 185:949-951, 1974.

9. Shwachman H, Kulczycki LL: A report of one hundred and five patients with cystic fibrosis of the pancreas studied over a five- to 14-year period. *Am J Dis Child* 96:6-15, 1958.

10. Mellits ED, Cheeks DB: The assessment of body water and fatness from infancy to adulthood. *Monogr Soc Res Child Dev* 35:12-27, 1970.

11. Pace N, Rathbun EN: Studies on body composition: III. The body water and chemically combined nitrogen content in relation to fat content. *J Biol Chem* 158:685-691, 1945.

12. Forbes GB: Methods for determining composition of the human body. *Pediatrics* 29:477-494, 1962.

13. Osler DC, Crawford JD: Examination of the hypothesis of a critical weight at menarche in ambulatory and bedridden mentally retarded girls. *Pediatrics* 51:675-679, 1973.

14. Crawford JD, Osler DC: Body composition at menarche: The Frisch-Revelle hypothesis revisited. *Pediatrics* 56:449-458, 1975.

15. Tanner JM: *Growth and Adolescence,* ed 2. Oxford, England, Blackwell Scientific Publications, 1962.

16. England BG, Niswender GD, Midgeley AR: Modification of radioimmunossay of 17B-estradiol without chromatography. *J Clin Endocrinol Metab* 38:42-50, 1974.

17. Mitchell-Heggs P, Mearns M, Batten JC: Cystic fibrosis in adolescents and adults. *Q J Med* 179:479-504, 1976.

18. Penny R, Goldstein IP, Frasier SD: Gonadotropin excretion and body composition. *Pediatrics* 61:294-300, 1978.

19. Johnson FE, Roche AF, Schell LM, et al: Critical weight at menarche. *Am J Dis Child* 129:19-23, 1975.

20. Frisch RE: Weight at menarche: Similarity for well nourished and undernourished girls at differing ages, and evidence for historical constancy. *Pediatrics* 50:445-450, 1972.

21. Forbes GB, Schwartz RH, Nelson LA: Body composition studies in patients with cystic fibrosis. *Cystic Fibrosis Club Abstracts* 20:41, 1979.

22. Boyar RM, Katz J, Finkelstein JW, et al: Anorexia nervosa: Immaturity of the 24-hour luteinizing hormone secretory pattern. *N Engl J Med* 291:861-865, 1974.

23. Warren MP: Weight loss and responsiveness to LH-RH, in Vigersky RA (ed): *Anorexia Nervosa.* New York, Raven Press, 1977, pp 189-198.

24. Reiter E, Stern R, Doershuk C, et al: Maturation of the reproductive endocrine system in cystic fibrosis. *Cystic Fibrosis Club Abstracts* 18:74, 1977.

Intravenous Aminophylline in Patients With Cystic Fibrosis

Pharmacokinetics and Effect on Pulmonary Function

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• Intravenous aminophylline was administered to ten patients with cystic fibrosis (CF) to determine if the medication would improve pulmonary function and to study theophylline pharmacokinetics. Intravenous normal saline was given on another day as a control. Thoracic gas volume and airway resistance, measured in a volume displacement body plethysmograph, and maximal expiratory flow-volume curves were performed before and after each infusion. No significant improvement was noted in pulmonary function after normal saline infusion. Following aminophylline infusion, significant improvement in thoracic gas volume, residual volume, specific airway conductance, and maximal expiratory flow at 60% of total lung capacity was noted. The pharmacokinetic analysis revealed a mean half-life of 4.7 hours, a total clearance of 91 mL/hr/kg, and a volume of distribution of 574 mL/kg. Intravenous aminophylline can acutely decrease airway obstruction in children with CF.

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The effect of methylxanthines on pulmonary function in patients with cystic fibrosis (CF) has been examined in one previous study, and theophylline was found to have limited usefulness when given orally over a four-week period.[1] We have assessed the short-term effects of intravenous (IV) aminophylline on pulmonary function in ten patients with CF and have found significant decreases in airway obstruction after the medication. In addition, the pharmacokinetic parameters of half-life, total clearance, and volume of distribution have been determined for each patient and for the group, and the results have been compared with published values for children with asthma.

PATIENTS AND METHODS

Ten children with CF were selected to be subjects for this study based on their ability to perform the required pulmonary function tests and willingness to participate in the study. Each patient had a forced expiratory volume in 1 s to forced vital capacity (FVC) ratio of less than 75%, indicating obstructive lung disease. The diagnosis of CF in all children was based on a sweat chloride concentration greater than 70 mEq/L with a consistent clinical and/or family history. In this study, there were six girls and four boys ranging in age from 10 to 18 years (Table 1). Their clinical National Institutes of Health (NIH) scores reflected mild to moderately severe disease.[2] An allergy profile for the patients showed that five had a clinical history compatible with allergic rhinitis, two had a history of at least one episode of wheezing, and nine had at least one positive skin test to common aeroallergens as determined in a previous prospective study.[3]

Each patient was studied on two separate days, when there was no clinical evidence of acute change in pulmonary status and no history of upper respiratory infection for a period of at least six weeks. On the first day, each patient was given a single dose of IV aminophylline equivalent to 4.0 mg/kg of theophylline (anhydrous) over five minutes. Because the study was also designed to measure theophylline kinetics in the subjects, and this required two IV lines and multiple blood samples totaling approximately 30 mL over eight hours, the patients knew they were receiving aminophylline. On the second study day, an equal volume of normal saline was given intravenously during a five-minute period. This part of the study was single-blind. Each patient was told he would receive either IV aminophylline or normal saline. All ten subjects, however, received normal saline so that the results of the pulmonary functions after the saline infusion could be compared with the results after aminophylline infusion. Thus, each child served as his own control. The patients and their parents gave informed consent before the study was performed.

On each study day, pulmonary function was tested before and 1, 3, and 5 hours after the infusion. A volume displacement body plethysmograph[4] was used to measure thoracic gas volume (TGV) and airway resistance,[5,6] and maximal expiratory flow-

volume curves were obtained with an electronic spirometer. Peak expiratory flow rate, together with maximal expiratory flow rate at 50% and 25% of the FVC ($\dot{V}_{max50}$, $\dot{V}_{max25}$), and maximal expiratory flow rate at 60% of total lung capacity (TLC) ($\dot{V}_{max60TLC}$) were measured. The ratio of residual volume (RV) to TLC was computed. Specific conductance of the airway was computed by dividing the reciprocal of resistance by the TGV. The plethysmography always preceded the maximal force expiratory maneuvers. A minimum of three plethysmographic measurements was performed, and the most reproducible and representative values were used for the calculations of TGV and airway resistance. The flow-volume curves were performed in triplicate, and the largest FVC was used to compute the flow rates. The RV was determined by subtracting the expiratory reserve volume from the TGV. The TLC was derived by adding the FVC and RV. All pulmonary function results were corrected to body temperature and pressure, saturated with water vapor.

Results of the pulmonary function tests were expressed as a percent change from baseline as well as a percent of predicted.[7-10] When expressed as a percent change from baseline, the results of pulmonary function measured at the same time after normal saline and aminophylline were analyzed for significant differences with the Wilcoxon signed rank test.[11] Results expressed as a percent of predicted were analyzed with a two-way analysis of variance and Dunnett's test for multiple comparisons[11] to determine if changes after either normal saline or aminophylline differed from the baseline pulmonary functions for that day.

Pharmacokinetics of theophylline were measured on the first study day. No subject was taking medication containing theophylline prior to the study, and all had abstained from foods and beverages containing xanthines for at least 48 hours prior to study. A single dose of aminophylline equivalent to 4.0 mg/kg of theophylline (anhydrous) was given at a constant rate by infusion pump for five minutes. Blood samples were obtained before injection and at 5, 10, 15, 20, 30, 40, 50, 60, 120, 180, 240, 360, and 480 minutes after the end of the injection. Serum theophylline levels were measured by high-pressure liquid chromatography using a modification of the method of Weddle and Mason.[12] Pharmacokinetic parameters (half-life, total clearance, and volume of distribution) were calculated from the best computer fit of the serum concentration-time curves obtained for each patient. The serum theophylline data were analyzed using MULTFIT, a nonlinear regression analysis program.[13] Without exception, the data from all subjects were best fitted by a bioexponential equation, corresponding to the well-established two-compartment model for theophylline distribution and elimination.

Blood drawn before the aminophylline infusion was also analyzed for γ-glutamyl transpeptidase and for transaminases (SGOT, SGPT) as indicators of hepatobiliary disease. γ-Glutamyl transpeptidase was determined by the method of Szasz,[14] whereas the method of Henry and associates[15] was used to assay the levels of SGOT and SGPT.

RESULTS

Significant decreases in airway obstruction after IV aminophylline were noted when the aminophylline response was compared with the saline response (Table 2) and also when the aminophylline response was compared with the baseline pulmonary functions before the infusion (Table 3). Compared with baseline, group mean values of TGV and RV decreased 24% to 37% ($P < .01$), whereas $\dot{V}_{max60TLC}$ increased from 35% at three hours ($P < .05$) to 64% at five hours ($P < .05$). In addition, aminophylline infusion increased specific conductance of the airway by 36% to 44% ($P < .02$ at one and three hours). The RV/TLC ratio decreased from 0.50 at baseline to 0.38 at three hours ($P < .01$). The TLC decreased from a mean of 122% of predicted at baseline to 102% of predicted at three and five hours after aminophylline infusion ($P < .01$).

An example of the type of changes in lung function found after administration of IV aminophylline is shown in Fig 1. The predicted flow-volume curve for patient 9 is plotted on an absolute lung-volume scale along with the curves at baseline and after IV aminophylline. Before aminophylline, the pattern of changes in pulmonary function in CF can be seen where TLC and RV are elevated, and the flow-volume curve is convex to the volume axis consistent with an obstructive lung disease. It can be seen that not only is the shape of the flow-volume curve abnormal, but flow at any absolute lung volume is markedly decreased. After aminophylline, the major change is a decrease in the obstruction manifest by a decrease in TGV and RV, an increase in vital capacity, and a variable decrease in the convexity of the flow-volume curve. Changes in pulmonary function such as this result in marked increases in flow rates at any absolute lung volume (Fig 1) with less marked but significant changes in flows related to the observed TLC at the time of each measurement. Flows related to vital capacity (eg, $\dot{V}_{max25}$) that do not take absolute lung volume into consideration will show no change or a small increase in flow.

Thoracic gas volume and RV, both expressed as a percent of predicted instead of percent change from baseline, are plotted in Fig 2 to illustrate

Table 1.—Profile of Patients Studied With Intravenous Aminophylline and Normal Saline

Patient No./ Age, yr/Sex	Height, cm	Weight, kg	NIH Score*	Allergy Profile: Positive† Skin Test	Allergy Profile: Allergic Rhinitis	Allergy Profile: Wheezing
1/15/F	161	43.5	64	2	+	—
2/10/F	144	31.9	86	3	+	—
3/18/F	158	41.0	92	12	—	—
4/13/M	137	30.5	83	0	—	—
5/12/M	153	33.6	73	2	+	—
6/12/M	142	26.4	72	1	+	+
7/14/F	158	47.0	85	9	—	—
8/16/F	165	49.0	85	9	+	+
9/16/M	168	52.5	88	2	—	—
10/11/F	137	30.4	92	1	—	—

*National Institutes of Health (NIH) score.[2] The maximum score of 100 indicates no evidence of disease by history, physical examination, roentgenogram, or pulmonary function test results.

†The 20 common aeroallergens evaluated with puncture tests; + indicates positive, —, negative.

the average degree of airway obstruction at baseline and the average reversibility. The RV was approximately 284% of predicted at baseline and had decreased to 177% of predicted at three hours, whereas TGV was 163% of predicted at baseline and fell to 117% of predicted at three hours (Table 3). These changes are significant ($P < .01$).

Although the mean increase in $\dot{V}_{max50}$ was 20% at five hours after IV aminophylline and the mean increase in vital capacity was 7.3% at three and five hours after the infusion, the improvement in these and the other pulmonary functions (airway resistance, peak expiratory flow rate) was less uniform and/or of less magnitude and therefore not statistically significant. On the other hand, all ten patients had at least a 13% decrease in TGV after the aminophylline infusion. After the normal saline infusion, only two children had a decrease in TGV, and the maximum decrease was only 4%. Again, this latter infusion was single-blind, and the patient did not know if he was receiving saline or aminophylline. All results for TGV are given in Table 4. The values of TGV had to be reproducible to be acceptable (ie, the three measurements at a given study time), and over 90% of the volumes given were reproducible to within ± 3%, with 50% of the volumes being exactly reproduced at the time of measurement.

The mean serum theophylline level at one hour was 5.8 μg/mL, with a range of 4.4 to 7.2 μg/mL, and at three hours the mean was 4.3 μg/mL, with a range of 3.0 to 6.3 μg/mL. Within this small, low range of serum theophylline levels, no correlation was found between serum drug level and the reversibility of the airway obstruction.

Table 5 is a listing of the individual half-lives, calculated from the elimination or β phase of the serum concentration-time curves. Also summarized in the table is the total clearance and volume of distribution for the subjects with CF. The individuals with abnormal results of liver function tests are indicated.

There was no correlation between the degree of improvement in lung function after IV aminophylline and the patient's age, number of positive skin tests, NIH score, or degree of pulmonary function abnormality at baseline.

COMMENT

Reversibility of the airways obstruction in patients with CF after bronchodilator therapy has been studied, but the published results and conclusions are conflicting.[1,16-25] These differences may be related to several factors. Isoproterenol hydrochloride has been the most frequently studied bronchodilator in patients with CF, but the dose, method of delivery, and

Table 2.—Percent Change in Pulmonary Function After Intravenous Aminophylline and Normal Saline*

Pulmonary Function	No. of Subjects	Time After Infusion, hr	Aminophylline	Sodium Chloride Irrigation	P
Thoracic gas volume	10	1	−24.1 ± 3.8	+6.1 ± 2.4	<.01
		3	−27.3 ± 3.2	+4.3 ± 2.0	<.01
		5	−26.3 ± 4.1	+5.3 ± 2.0	<.01
Residual volume	10	1	−30.5 ± 3.7	+11.3 ± 3.4	<.01
		3	−37.7 ± 3.8	+2.7 ± 3.8	<.01
		5	−36.3 ± 4.9	+7.4 ± 2.4	<.01
$\dot{V}_{max60TLC}$	6†	1	+35.2 ± 9.6	−28.3 ± 7.6	<.05
		3	+54.7 ± 15.0	−5.5 ± 7.1	<.05
		5	+64.0 ± 20.4	−7.8 ± 6.9	<.05
$\dot{V}_{max25}$	10	1	+22.4 ± 13.1	−10.8 ± 8.5	<.02
		3	+5.3 ± 7.5	−3.2 ± 5.3	NS
		5	+14.3 ± 5.8	−2.5 ± 7.8	NS
Specific conductance of airway	10	1	+43.9 ± 18.4	+2.0 ± 3.6	<.02
		3	+44.2 ± 17.0	+2.8 ± 3.8	<.01
		5	+35.8 ± 9.9	+10.1 ± 5.1	NS

*Values represent mean ±1 SEM of percent change from baseline after intravenous aminophylline or sodium chloride irrigation. $\dot{V}_{max60TLC}$ indicates maximal expiratory flow rate at 60% of total lung capacity (TLC); $\dot{V}_{max25}$ indicates maximal expiratory flow rate at 25% of forced vital capacity.
†Four patients had a baseline residual volume-total lung capacity ratio greater than 0.60.

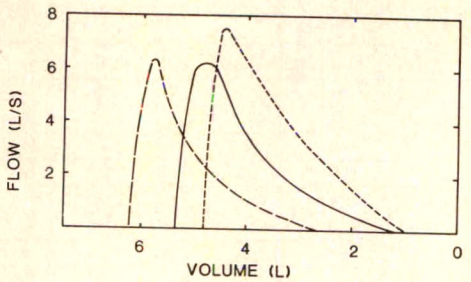

Fig 1.—Predicted (short dashes), baseline (long dashes), and posttreatment (continuous line) pulmonary functions for patient 9, using flow-volume curves placed on absolute lung-volume axis. Total lung capacity is at extreme left of each curve; residual volume at extreme right.

time of testing after delivery of medication have varied from one study to another.[17,19,20,22-25] In addition, only two previous studies of inhaled bronchodilators controlled the evaluation by repeating pulmonary functions using the same test conditions without a bronchodilator.[20,26] Two uncontrolled studies[23,25] found that maximal expiratory flows could decrease after isoproterenol inhalation in patients with CF, leading to the suggestion that isoproterenol might be causing the decreased flows by decreasing smooth-muscle tone of airways, thereby allowing greater collapse of airways during a forced expiration. Though this argument may be valid, the need for controlled studies of bronchodilator effect in CF is supported by the observations of Lifshitz and Denning[20] and of Larsen et al,[26] who showed that repeated pulmonary function maneuvers may cause decreased flows and increased gas trapping in patients with CF. This was again noted in this study, where flows tended to decrease while TGV and RV usually increased or became more abnormal in the control study (Table 2).

Several studies of bronchodilators in CF have evaluated pulmonary function parameters that are less sensitive indicators of the small airway disease than are those used in the present study.[17,19,20] From the work of Cooper and associates,[27] the most sensitive tests for detecting abnormalities in CF include RV/TLC ratio and $\dot{V}_{max60TLC}$. For both lung functions, absolute lung volumes must be known.

In order to overcome some of the problems of earlier studies, the present study used a controlled protocol where subjects were retested in a blind manner with IV saline alone. In addition, a dose of medication based on the weight of the patient was administered by the IV route to avoid possible problems caused by different rates and degrees of absorption of oral medicine. Furthermore, information from both a body plethysmograph and flow-volume curve were employed in evaluating responses so that we could assess changes in absolute lung volumes and flows related to these lung volumes. This latter aspect of our study may explain the difference between our results and those of Shapiro and co-workers, who found no consistent beneficial response to oral theophylline.[1] The larger postaminophylline increase in flow, when related to TLC noted in this study, and the lack of significant change in most flows related to vital capacity in both this study and the study of Shapiro and associates,[1] are explained by the simultaneous change in TGV and RV after aminophylline. It is only when absolute lung volumes are examined

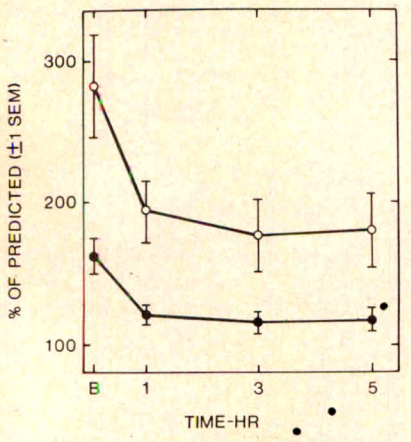

Fig 2.—Mean values (± 1 SEM) for residual volume (open circles) and thoracic gas volume (closed circles) expressed as percent of predicted at baseline (B) and 1, 3, and 5 hours after intravenous aminophylline.

Table 3.—Pulmonary Function Expressed as Percent of Predicted at Baseline (B) and After Aminophylline, Mean ± 1 SEM*

Pulmonary Function	No. of Subjects	Time, hr	Aminophylline	P
Thoracic gas volume	10	B	162.9 ± 13.3	
		1	120.6 ± 7.6	< .01
		3	116.5 ± 8.4	< .01
		5	117.0 ± 8.2	< .01
Residual volume	10	B	283.9 ± 36.3	
		1	193.3 ± 22.9	< .01
		3	177.4 ± 25.8	< .01
		5	179.1 ± 25.7	< .01
$\dot{V}_{max60TLC}$	6	B	56.3 ± 14.2	
		1	74.0 ± 16.6	< .01
		3	80.2 ± 16.1	< .01
		5	84.7 ± 17.8	< .01
Specific conductance of airway	10	B	53.2 ± 7.2	
		1	71.0 ± 8.4	< .05
		3	71.8 ± 8.6	< .05
		5	71.1 ± 10.3	< .05

*P values at 1, 3, and 5 hours refer to difference between baseline value before aminophylline and value at specified time after aminophylline. $\dot{V}_{max60TLC}$ indicates maximal expiratory flow rate at 60% of total lung capacity.

Table 4.—Thoracic Gas Volume (L) Before and After Intravenous Aminophylline and Normal Saline

		Aminophylline				Saline			
Patient	Predicted*	Baseline	1 hr	3 hr	5 hr	Baseline	1 hr	3 hr	5 hr
1	1.95	3.96	3.32	3.32	3.56	3.83	3.83	3.96	3.83
2	1.52	1.85	1.49	1.60	1.44	1.98	2.12	2.28	2.36
3	1.88	2.36	2.28	2.05	2.05	2.83	2.83	2.73	2.94
4	1.39	1.44	1.19	1.10	1.29	1.44	1.78	1.39	1.49
5	1.80	4.40	2.38	2.57	2.29	2.67	2.98	2.98	2.77
6	1.39	2.63	1.72	1.91	1.60	2.29	2.48	2.48	2.38
7	1.88	2.88	1.93	1.85	1.93	2.38	2.38	2.57	2.38
8	2.16	3.83	2.98	2.48	2.88	3.83	4.10	3.83	3.83
9	2.32	3.83	2.98	2.57	2.48	4.10	4.10	4.25	4.25
10	1.27	1.85	1.34	1.24	1.34	1.44	1.49	1.44	1.66

*Based on normal values in Polgar and Promadhat.[7]

that a consistent beneficial effect of the aminophylline is noted.

The importance of examining patients with obstructive lung disease for changes in lung volumes has been pointed out by Woolcock and Read,[28] who noted that some patients clinically recovering from asthma will not show significant improvement in flows on a spirogram but will have marked decreases in TLC and RV, reflecting a decrease in the degree of hyperinflation. Their illustration of these changes, shown by placing the volume-time tracing (spirogram) on an absolute lung-volume scale, is similar to Fig 1, where flow-volume curves are examined on an absolute lung-volume scale. Benatar and Konig[29] have also employed maximal expiratory flow-volume curves on an absolute lung-volume axis to study the response of asthmatics to exercise and bronchodilators. They also noted that in some subjects, changes in RV and TLC developed without a change in the slope of the maximal expiratory flow-volume curve. They believed that lung-volume changes might reflect functional closure of some lung units, whereas changes in slope of the curve would reflect changes in the time constants in the lung. Based on this interpretation, the parallel shifts in the flow-volume curve with variable improvement in slope might mean that the major effect of this IV dose of aminophylline in these patients with CF was to decrease peripheral airway obstruction and thus decrease functional closure of some lung units. More detailed studies would be needed to address this point.

Recently, Ramsdell and Tisi[30] have reemphasized the importance of including measurements of static lung volumes in assessing pulmonary response to bronchodilators. In patients with obstructive lung disease who responded to isoproterenol inhalation, they found that 41% exhibited bronchodilation by significantly improving static lung volumes without improving expiratory flows. In contrast, 44% had significant changes in expiratory flow but not in lung volume, whereas 15% showed improvement in both flows and volumes. In general, the subjects showing only volume changes had more severe airway obstruction and hyperinflation at baseline. They pointed out that if a response had been assessed only in terms of increased expiratory flows, improvement would have been overlooked in several of the patients. Based on the changes in lung function noted in this study, observations for changes in lung volumes in patients with CF may be very important in assessing response to bronchodilators.

Nine of the ten patients studied had at least one positive skin test to common inhaled aeroallergens. A high incidence of positive skin tests in CF has been reported.[3,31,32] Warner et al[32] have suggested that the atopy may be secondary to impaired handling of antigen at a mucosal surface. In our population of children with CF, we would expect over 60% to have at least one positive skin test to common aeroallergens.[3] We found no correlation between the number of positive skin tests and the reversibility of the airway obstruction. Further support for the nonspecific nature of positive skin tests in CF was recently reported by Mellis and Levison, who found that positive response to inhaled histamine in patients with CF correlated with abnormal pulmonary functions but not with positive skin tests.[33] Another study from the same laboratory came to the same conclusion after studying methacholine responses in patients with CF.[34] In addition, Nelson et al have recently interpreted the increased skin reactivity in CF as representing increased sensitization from allergen contact with a more permeable, damaged respiratory epithelium.[35] Therefore, the fact that most subjects tested had positive skin tests does not necessarily mean that their airways are more likely to respond to bronchodilators. However, more subjects with no skin-test reactivity would have to be studied to address that question.

The serum theophylline levels that were measured one and three hours after the IV infusion were lower than the commonly recommended therapeutic levels of 10 to 20 μg/mL.[36] However, as previously reported by Maselli and co-workers, therapeutic effects of theophylline can be seen with low serum levels in childhood asthma.[37] It remains to be determined if higher plasma concentrations in patients with CF would further decrease pulmonary function abnormalities.

The pharmacokinetic analysis provided both individual and mean values for theophylline half-lives, total clearances, and volume of distribution (Table 5). These values can be compared with similar published results for children with asthma. Ellis et al[38] found that 30 asthmatic children of similar age to those we studied had a half-life value of 3.69 ± 1.13 hours, with a range of 1.42 to 7.85 hours. This mean value is shorter than the half-life of 4.66 ± 1.10 hours for the patients with CF, but the range for our group of patients is again wide (3.08 to 6.15 hours), reflecting large interindividual variation. Total clearances were similar in both studies (91 mL/hr/kg in CF vs 87 mL/hr/kg in asthma), but again much interindividual variation was noted. The volume of distribution, however, for children with CF

Table 5.—Pharmacokinetics of Theophylline in Patients With Cystic Fibrosis

Patient	Half-life, hr	Total Clearance, mL/hr/kg	Volume of Distribution, mL/kg
1	3.08	116	517
2	4.76	78	532
3*	5.82	64	539
4	5.15	83	614
5*	4.49	98	636
6	3.35	147	709
7	3.75	103	559
8	4.10	97	576
9*	6.15	54	476
10*	5.94	68	580
Mean ± 1 SD	4.66 ± 1.10	91 ± 28	574 ± 66

*Patients with abnormal liver function tests results.

(574 ± 66 mL/kg) was significantly larger ($P < .01$) than the value reported for children with asthma (422 ± 64 mL/kg). A diminished volume of distribution for theophylline has been previously attributed to obesity.[39] It is therefore reasonable to assume that the decreased adipose tissue in patients with CF could result in the larger volume of distribution per unit of body weight.

Because theophylline is metabolized in the liver, we wanted to determine if the pharmacokinetic variability was related to liver function. Kattwinkel and co-workers[40] found abnormal results of liver function tests in 15 of 40 (37.5%) patients with CF. We found evidence of hepatic dysfunction in four of our ten subjects based on abnormal serum elevations for age of γ-glutamyl transpeptidase, SGOT, and/or SGPT. The patients with abnormal test results are noted in Table 5, and as can be seen, those subjects with serologic abnormalities generally had the longest half-lives and the lowest clearances for this drug. This high incidence of hepatic dysfunction and interindividual variation in kinetics emphasize the point that theophylline dosage regimens in children with CF must be individualized and carefully monitored if this drug is used clinically.

Georgia Wheeler helped in the preparation of the Manuscript and Gary Zerbe, PhD, helped in the statistical analysis.

References

1. Shapiro GG, Bamman J, Kanarek P, et al: The paradoxical effect of adrenergic and methylxanthine drugs in cystic fibrosis. *Pediatrics* 58:740-743, 1976.
2. Taussig LM, Kattwinkel J, Friedewald WT, et al: A new prognostic score and clinical evaluation system for cystic fibrosis. *J Pediatr* 82:380-390, 1973.
3. Barron R, Cotton E, Larsen G, et al: The prevalence of atopy in cystic fibrosis, abstracted. *Am Rev Respir Dis* 115 (pt 2):275, 1977.
4. Mead J: Volume displacement body plethysmograph for respiratory measurements in human subjects. *J Appl Physiol* 15:736-740, 1960.
5. DuBois AB, Botelho SY, Bedell GN, et al: A rapid plethysmographic method for measuring thoracic gas volume: A comparison with nitrogen washout method for measuring functional residual capacity in normal subjects. *J Clin Invest* 35:322-326, 1956.
6. DuBois AB, Botelho SY, Comroe JH: A new method for measuring airway resistance in man using a body plethysmograph: Values in normal subjects and patients with respiratory disease. *J Clin Invest* 35:327-335, 1956.
7. Polgar G, Promadhat V: *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia, WB Saunders Co, 1971, chap 5.
8. Weng TR, Levison H: Standards of pulmonary function in children. *Am Rev Respir Dis* 99:879-894, 1969.
9. DeMuth GR, Howatt WF, Hill B: V. Forced flow rates. *Pediatrics* 35:200-210, 1965.
10. Zapletal A, Motoyama EK, van de Woestijne KP, et al: Maximum expiratory flow-volume curves and airway conductance in children and adolescents. *J Appl Physiol* 26:308-316, 1969.
11. Steel RGD, Torrie JH: *Principles and Procedures of Statistics*. New York, McGraw-Hill Book Co, 1960, chap 7, 21.
12. Weddle OH, Mason WD: Rapid determination of theophylline in human plasma by high-pressure liquid chromatography. *J Pharm Sci* 65:865-868, 1976.
13. Smolen VF: Theoretical and computational basis for drug bioavailability determinations using pharmacological data: I. General considerations and procedures. *J Pharmacokinet Biopharm* 4:337-353, 1976.
14. Szasz G: A kinetic photometric method for serum γ-glutamyl transpeptidase. *Clin Chem* 15:124-136, 1969.
15. Henry RJ, Chiamori N, Golub OJ, et al: Revised spectrophotometric methods for determination of glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and lactic dehydrogenase. *Am J Clin Pathol* 34:381-398, 1960.
16. West JR, Levin SM, di Sant'Agnese PA: Pulmonary function in cystic fibrosis of the pancreas. *Pediatrics* 13:155-164, 1954.
17. Gandevia B, Anderson C: The effect of a bronchodilator aerosol on ventilatory capacity in fibrocystic disease of the pancreas. *Arch Dis Child* 34:511-515, 1959.
18. Mellins RB, Levine OR, Ingram RH, et al: Obstructive disease of the airways in cystic fibrosis. *Pediatrics* 41:560-573, 1968.
19. Mearns MB: Simple tests of ventilatory capacity in children with cystic fibrosis. *Arch Dis Child* 43:528-539, 1968.
20. Lifshitz MI, Denning CR: Assessment of bronchospasm in patients with cystic fibrosis. *Am Rev Respir Dis* 99:399-405, 1969.
21. Phelan PD, Gracey M, Williams HE, et al: Ventilatory function in infants with cystic fibrosis. *Arch Dis Child* 44:393-400, 1969.
22. Featherby EA, Weng T, Levison H: The effect of isoproterenol on airway obstruction in cystic fibrosis. *Can Med Assoc J* 102:835-838, 1970.
23. Zapletal A, Motoyama EK, Gibson LE, et al: Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics* 48:64-72, 1971.
24. Chang N, Levison H: The effect of a nebulized bronchodilator administered with and without intermittent positive pressure breathing on ventilatory function in children with cystic fibrosis and asthma. *Am Rev Respir Dis* 106:867-872, 1972.
25. Landau LI, Phelan PD: The variable effect of a bronchodilating agent on pulmonary function in cystic fibrosis. *J Pediatr* 82:863-868, 1973.
26. Larsen GL, Barron RJ, Cotton EK, et al: A comparative study of atropine sulfate and isoproterenol hydrochloride in cystic fibrosis. *Am Rev Respir Dis* 119:399-407, 1979.
27. Cooper DM, Doron I, Mansell AL, et al: The relative sensitivity of closing volume in children with asthma and cystic fibrosis. *Am Rev Respir Dis* 109:519-524, 1974.
28. Woolcock AJ, Read J: Improvement in bronchial asthma not reflected in forced expiratory volume. *Lancet* 2:1323-1325, 1965.
29. Benatar SR, Konig P: Maximal expiratory flow and lung volume changes associated with exercise-induced asthma in children and the effect of breathing a low-density gas mixture. *Clin Sci Mol Med* 46:317-329, 1974.
30. Ramsdell JW, Tisi GM: Determination of bronchodilation in the clinical pulmonary function laboratory: Role of change in static lung volumes. *Chest* 76:622-628, 1979.
31. Allan JD, Moss AD, Wallwork JC, et al: Immediate hypersensitivity in patients with cystic fibrosis. *Clin Allergy* 5:255-261, 1975.
32. Warner JO, Taylor BW, Norman AP, et al: Association of cystic fibrosis with allergy. *Arch Dis Child* 51:507-511, 1976.
33. Mellis CM, Levison H: Bronchial reactivity in cystic fibrosis. *Pediatrics* 61:446-450, 1978.
34. Mitchell I, Corey M, Woenne R, et al: Bronchial hyperreactivity in cystic fibrosis and asthma. *J Pediatr* 93:744-748, 1978.
35. Nelson LA, Callerame ML, Schwartz RH: Aspergillosis and atopy in cystic fibrosis. *Am Rev Respir Dis* 120:863-873, 1979.
36. Piafsky KM, Ogilvie RI: Dosage of theophylline in bronchial asthma. *N Engl J Med* 292:1218-1222, 1975.
37. Maselli R, Casal GL, Ellis EF: Pharmacologic effects of intravenously administered aminophylline in asthmatic children. *J Pediatr* 76:777-782, 1970.
38. Ellis EF, Koysooko R, Levy G: Pharmacokinetics of theophylline in children with asthma. *Pediatrics* 58:542-547, 1976.
39. Gal P, Jusko WH, Yurchak AM, et al: Theophylline deposition in obesity. *Clin Pharmacol Ther* 23:438-444, 1978.
40. Kattwinkel J, Taussig LM, Statland BE, et al: The effects of age on alkaline phosphatase and other serologic liver function tests in normal subjects and patients with cystic fibrosis. *J Pediatr* 82:234-242, 1973.

Pneumatosis Intestinalis

Its Occurrence in the Immunologically Compromised Child

Paul K. Kleinman, MD; Paula W. Brill, MD; Patricia Winchester, MD

• Four immunologically compromised children, two with acute lymphoblastic leukemia who received immunosuppressive therapy, one with X-linked agammaglobulinemia, and one with chronic granulomatous disease of childhood, displayed both the pulmonary and gastrointestinal mechanisms that led to pneumatosis intestinalis. Consideration of both the basic disease and the immediate clinical circumstances that surround the development of intramural air are helpful in the determination of the significance of pneumatosis intestinalis in individual patients.

(*Am J Dis Child* 134:1149-1151, 1980)

Necrotizing enterocolitis is the most frequent cause of pneumatosis intestinalis in the neonate.[1] In the older child, this condition is uncommon and usually occurs in association with a serious underlying disease. The presence of intramural gas may reflect structural alterations in the bowel wall. It may also arise by transdiaphragmatic dissection of extra-alveolar air in patients with lung disease.[2-7] In patients with congenital or acquired immunodeficiency, localization of the source of the intramural gas may be difficult. Thus, an understanding of potential causes and mechanisms that give rise to intramural intestinal air aids in assessment of the significance of pneumatosis intestinalis in the immunologically compromised patient.

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REPORT OF CASES

Case 1.—An 11-year-old boy, with X-linked agammaglobulinemia and a history of recurrent pneumonia, showed pneumatosis intestinalis and pneumomediastinum on roentgenograms taken during evaluation of an acute respiratory infection (Fig 1). There were no abdominal complaints. Resolution of the abnormal air collections was documented on follow-up roentgenograms three weeks later.

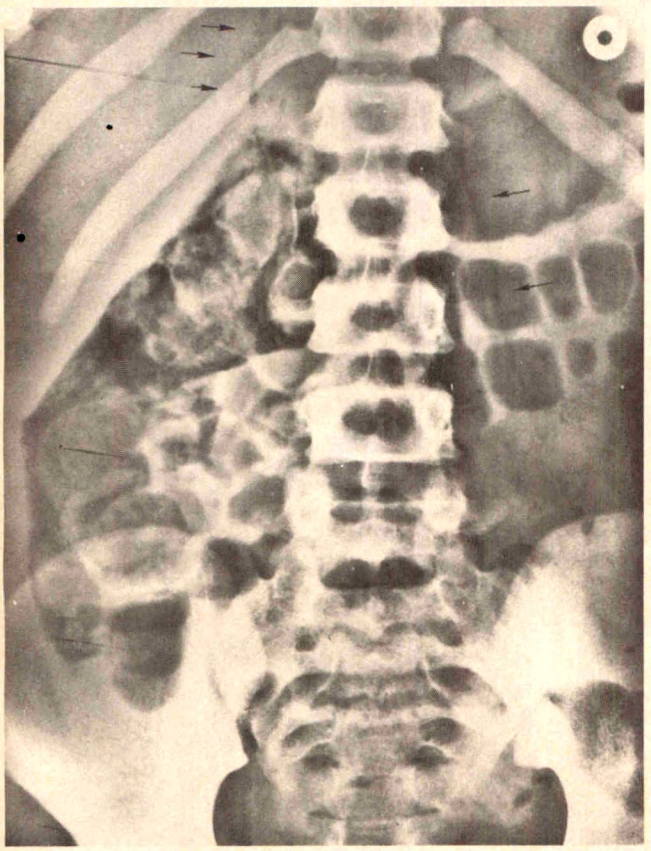
Case 2.—A 14-year-old girl with acute lymphoblastic leukemia in relapse had cavitary lung lesions, probably due to *Aspergillus*. She received prednisone and cytotoxic agents for the leukemic relapse and amphotericin B for the *Aspergillus* infection. The lung lesions diminished, but some were still present when right upper quadrant pain and abdominal distention developed. Pneumatosis intestinalis as well as retroperitoneal air were demonstrated on a roentgenogram of the abdomen (Fig 2). Symptoms abated within two days, and the pneumatosis intestinalis and retroperitoneal and mediastinal air resolved in two weeks.

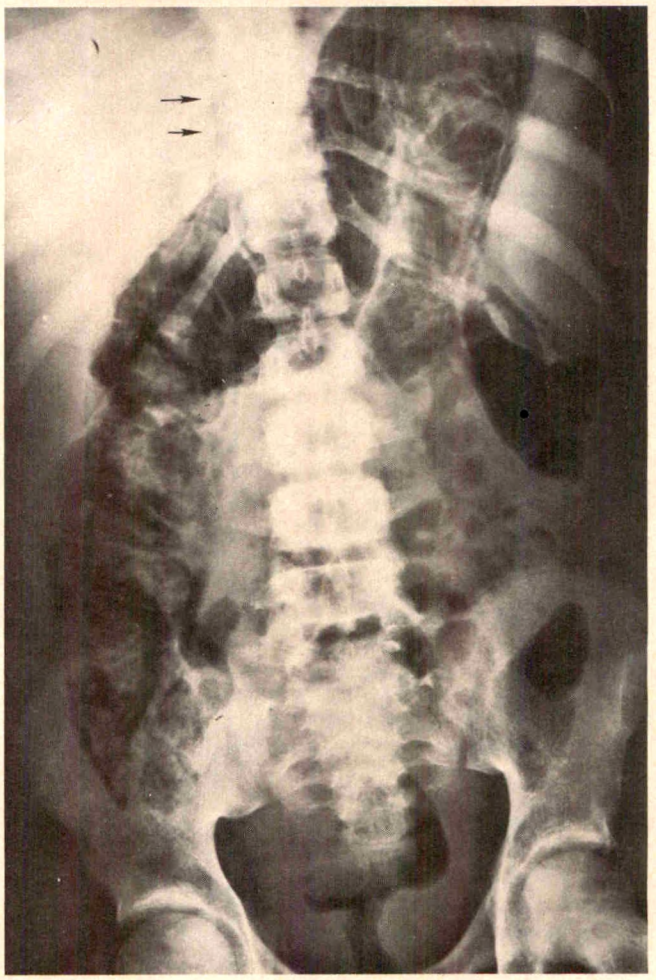
Case 3.—A 5-year-old boy with chronic granulomatous disease had acute abdominal distention and watery diarrhea during the course of treatment for staphylococcal pneumonia. An abdominal roentgenogram demonstrated pneumatosis intestinalis (Fig 3). *Salmonella enteritidis*, type infantis, grew from cultures of stool, ascitic fluid, and blood. Chest roentgenograms showed no evidence of extra-alveolar air. Diarrhea and distention resolved with the institution of therapy with gentamicin sulfate and ampicillin sodium. The pneumatosis intestinalis was not visible eight days after its initial identification.

Case 4.—A 14-month-old boy (previously mentioned by Meyers et al[6]) with acute lymphoblastic leukemia in remission was admitted to the hospital with fever and dehydration after five days of severe, watery diarrhea. The abdomen was soft and cultures of stool initially grew normal flora. Methicillin sodium, gentamicin, and ampicillin were given because of the possibility of a rectal abscess. Diarrhea continued, and on three occasions enteropathogenic *Escherichia coli* were recovered from the stool. Eleven days after admission, an abdominal roentgenogram showed extensive pneumatosis intestinalis that involved the descending colon and rectosigmoid. The pneumatosis gradually decreased with the institution of therapy with colistin sulfate. Diarrhea and fever resolved, and subsequent cultures of stool were negative for pathogens.

COMMENT

Pneumatosis intestinalis may arise by dissection of intraluminal gas into





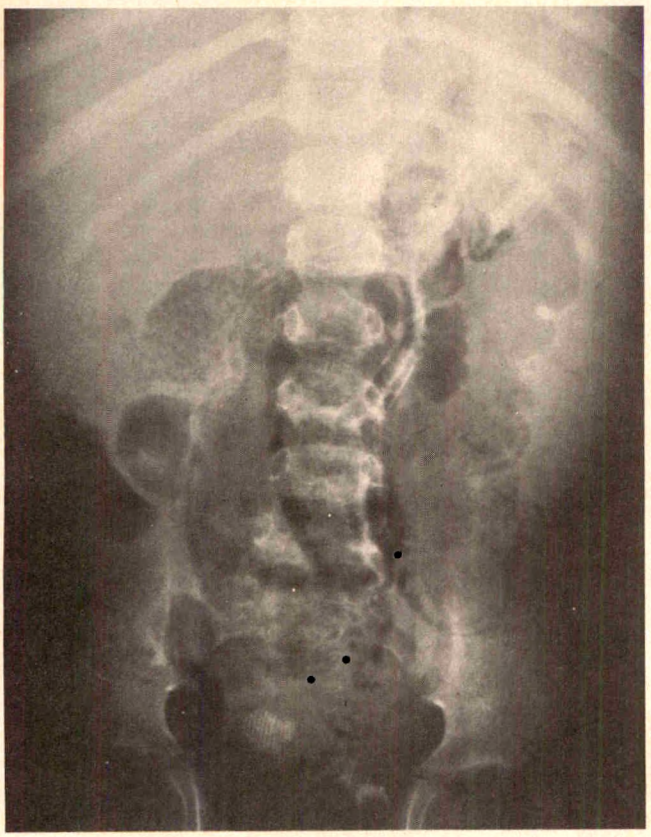


Fig 1 (top, left).—Case 1. Extensive pneumatosis intestinalis of right colon: retroperitoneal air is present in right suprarenal region and along left psoas margin (arrows).

Fig 2 (top, right).—Case 2. Extensive pneumatosis throughout ascending and transverse colon. Linear collections extend into interhaustral folds. Retroperitoneal air outlines right diaphragmatic crus (arrows).

Fig 3 (bottom).—Case 3. Supine abdominal roentgenogram on 5-year-old boy with chronic granulomatous disease and *Salmonella* enterocolitis. Linear pneumatosis intestinalis involves colon in midabdomen and left abdomen. Intramural air extends into interhaustral folds of lateral margin of descending colon. No evidence of retroperitoneal air is present.

the bowel wall secondary to mechanical or ischemic mucosal injury. Enteric organisms may contribute to this gaseous accumulation. This mechanism explains its development in neonatal necrotizing enterocolitis,[1] as well as in inflammatory or ischemic bowel disease in older children.[8-10] It may also occur secondary to structural alterations of the bowel wall without actual ischemic injury, providing access of intraluminal gas to the submucosa. This mechanism has been proposed for the development of pneumatosis intestinalis in patients with leukemia who have depleted lymphoid tissue secondary to immunosuppressive therapy.[11] Pneumatosis intestinalis has also been noted in patients with collagen vascular disease.[12] Structural alterations without ischemia may explain its occurrence in these patients[13]; however, compromise of splanchnic blood flow secondary to vasculitis also plays a significant role in some cases.[8]

Pneumatosis intestinalis may also arise from pulmonary air leakage. Air arising from alveolar rupture with dissection along the perivascular planes to the mediastinum can extend transdiaphragmatically, ultimately to an intramural intestinal location.[5] This transdiaphragmatic extension can occur posteriorly through the aortic hiatus of the diaphragm, as well as anteriorly through the Morgagni's foramina.[14] This mechanism likely explains its occurrence in children with cystic fibrosis and other forms of pulmonary disease that lead to air-block phenomena.[2-7]

The presence of pulmonary disease and the lack of intra-abdominal signs and symptoms suggest that the chest was the source of the pneumatosis intestinalis in cases 1 and 2. In case 3, with both staphylococcal pneumonia and *Salmonella* enterocolitis, the source could have been either pulmonary or intestinal. Case 4 is especially interesting as this patient had pneumatosis intestinalis in the face of severe enterocolitis due to enteropathogenic *E coli*. Though structural alterations of the bowel wall due to immunosuppressive therapy may have predisposed to the development of the intramural intestinal air, the infectious process probably played a significant role.

The significance of pneumatosis intestinalis in any given case is best understood by a consideration of the ways in which the underlying disease and its therapy may alter the bowel wall and by an awareness that superimposed disease in either the chest or abdomen may be the source of intramural gas.

Nonproprietary Names and Trademarks of Drugs

Amphotericin B—*Fungizone.*
Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Pen A/N, Penbritin-S for Injection.*
Gentamicin sulfate—*Garamycin, Genoptic.*

References

1. Berdon WE, Grossman H, Baker DH, et al: Necrotizing enterocolitis in the premature infant. *Radiology* 83:879-887, 1964.
2. Crider RJ Jr, Bentlif P: Pneumatosis cystoides intestinalis: The report of a case associated with severe pulmonary disease and chronic lymphocytic leukemia. *Henry Ford Hosp Med J* 17:285-294, 1969.
3. Jaffe N, Carlson DH, Vawter GF: Pneumatosis cystoides intestinalis in acute leukemia. *Cancer* 60:239-243, 1972.
4. Keats TE, Smith TH: Benign pneumatosis intestinalis in childhood leukemia. *AJR* 122:150-152, 1974.
5. Keyting WS, McCarver RR, Kovarik JL, et al: Pneumatosis intestinalis: A new concept. *Radiology* 76:733-741, 1961.
6. Meyers MA, Ghahremani GG, Clements JL Jr, et al: Pneumatosis intestinalis. *Gastrointest Radiol* 2:91-105, 1977.
7. Wood RE, Merman CJ, Johnson KW, et al: Pneumatosis coli in cystic fibrosis. *Am J Dis Child* 129:246-248, 1975.
8. Kleinman P, Meyers MA, Abbott G, et al: Necrotizing enterocolitis with pneumatosis intestinalis in systemic lupus erythematosus and polyarteritis. *Radiology* 121:595-598, 1976.
9. Kleinman PK, King DR: Necrotizing jejunitis and pneumatosis intestinalis secondary to anastomotic obstruction following jejunal atresia repair. *Gastrointest Radiol* 2:113-115, 1977.
10. Kleinman PK, Winchester P, Brill PW: Necrotizing enterocolitis after open heart surgery employing hypothermia and cardiopulmonary bypass. *AJR* 127:757-760, 1976.
11. Borns PF, Johnston TA: Indolent pneumatosis of the bowel wall associated with immune suppressive therapy. *Ann Radiol* 16:163-166, 1973.
12. Mueller CF, Morehead R, Alter AJ, et al: Pneumatosis intestinalis in collagen disorders. *AJR* 155:300-305, 1972.
13. Freiman D, Hikon C, Larissa B: Pneumatosis intestinalis in systemic lupus erythematosus. *Radiology* 116:563-564, 1975.
14. Kleinman PK, Brill PW, Whalen JP: Anterior pathway for transdiaphragmatic extension of pneumomediastinum. *AJR* 131:271-275, 1978.

Necrotizing Enterocolitis

Epidemic Following an Outbreak of *Enterobacter cloacae* Type 3305573 in a Neonatal Intensive Care Unit

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• Twelve cases of necrotizing enterocolitis (NEC) occurred within three weeks in a neonatal intensive care unit (NICU) with 325 annual admissions. *Enterobacter cloacae* type 3305573 was found in stool and/or blood cultures from affected babies prior to the onset of the disease. This bacterium could not be grown in cultures from infants in the same NICU six weeks later. A causal relationship between *E cloacae* and the epidemic of NEC is suggested.

(*Am J Dis Child* 134:1152-1154, 1980)

The precise etiology and pathophysiology of necrotizing enterocolitis (NEC) remain unclear, but several observations have supported the role of an infectious agent in its pathogenesis. A few epidemics of NEC have been reported[1-7] and these have been associated with various enteropathogenic bacteria such as *Escherichia coli*,[2] *Klebsiella pneumoniae*,[3] *Salmonella*,[4] and *Clostridium butyricum*.[5] Three other reports of epidemics of NEC failed to incriminate a particular pathogen.[1,6,7] Recently, it has been suggested that recognition of NEC as a potentially epidemic disease and implementation of infection control measures can decrease the incidence of NEC.[7] We report an epidemic of NEC in our neonatal intensive care unit (NICU) and its association with a nosocomial infection with *E cloacae* type 3305573.

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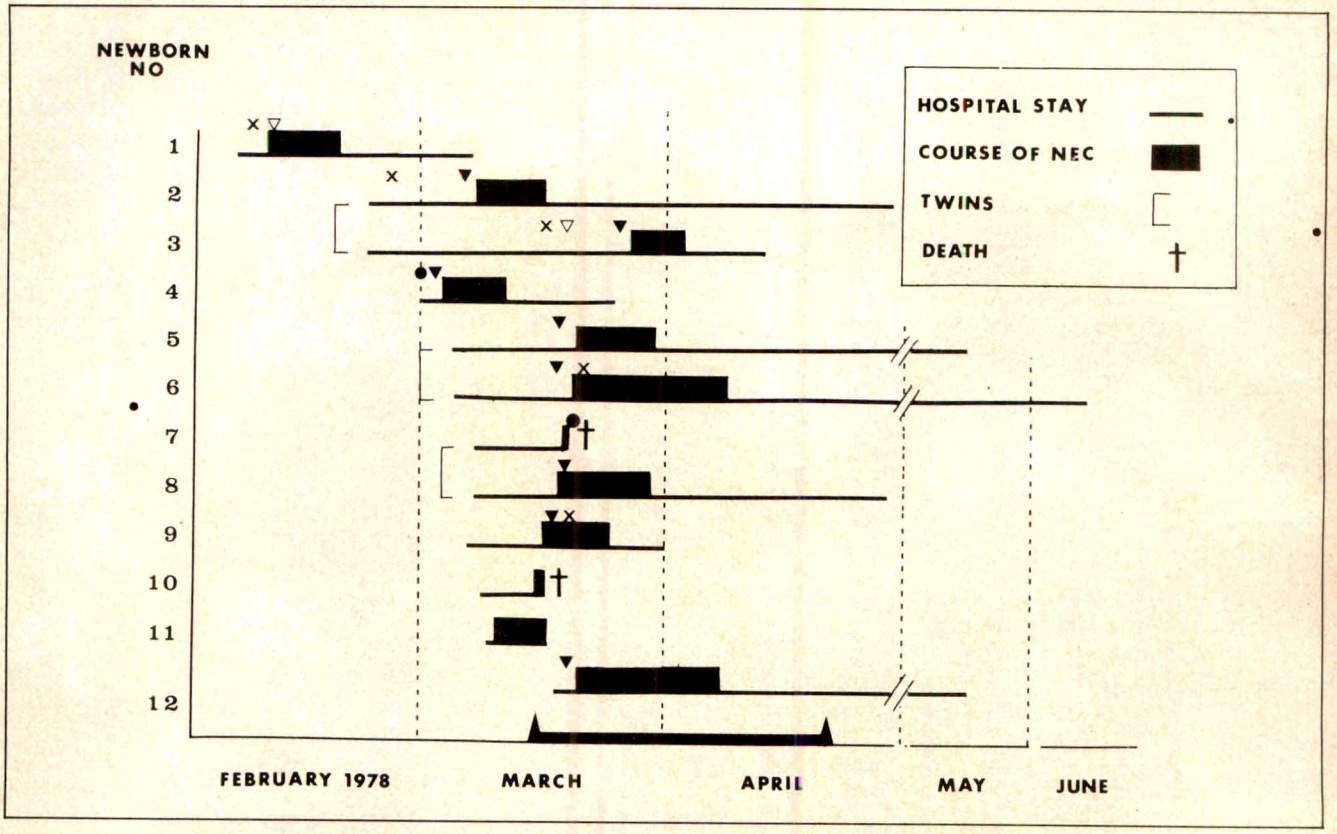
DESCRIPTION OF EPIDEMICS

Twelve cases of NEC occurred at the NICU of the Centre Hospitalier Universitaire de Sherbrooke during February and March 1978, and 11 of these occurred within the 18-day period from March 3 to 21 (Fig 1). This represents 32% of all admissions to our NICU for that period (11/34). In the two months preceding and in the two months following the epidemic of NEC, there were no other cases of NEC in the unit. There were only three patients with NEC in 1977 and six (excluding the epidemic) in 1978.

All of the babies involved in the epidemic of NEC were premature (mean gestational age, 33.3 weeks; mean weight, 1,667 g), either born at our hospital (4/12) or referred because of prematurity and/or respiratory distress syndrome (8/12). All of these had the classic[8] clinical and radiological features of NEC. Clinical signs were as follows: abdominal distention (ten patients); feeding intolerance (eight); gastrointestinal (GI) tract bleeding (eight); diarrhea (three); hypotension (two); and apnea (five). Radiological signs were as follows: intestinal distention (local or generalized) (12); pneumatosis intestinalis (ten); pneumoperitoneum (two); and portal venous gas (one). The mean age at which these were first observed was 10.3 days. Their predisposing factors, as reported by others,[1,2] included prematurity, (12/12); hyaline membrane disease (11/12); perinatal shock (10/12); and placement of an arterial umbilical catheter (9/12). Eight of the 12 patients had been fed cow's milk formula (Similac), and four, human milk. After the diagnosis of probable or definite NEC was made for each patient, the treatment consisted of total parenteral nutrition and parenteral antibiotic therapy (ampicillin trihydrate, 100 mg/kg/day, gentamicin sulfate, 5 mg/kg/day), bicarbonate infusion, and fresh blood transfusions when blood hemoglobin concentration was 10 g/dL or below. Surgery was necessary in two patients who had bowel perforation. One of these died shortly after surgery; the



Schematic presentation of temporal relationship among 12 patients with necrotizing enterocolitis (NEC). Timing of positive initial stool culture for *Enterobacter cloacae* type 3305573 is given by closed triangles; negative results, open triangles; circles indicate positive blood cultures; X, recovery of *E cloacae* from various sites of culture (trachea, pharynx, etc); heavy bar on abscissa, period of special infection control measures.

second (a fulminant case) died before operation could be performed. The other ten newborns recovered from their NEC without sequelae.

With the first four patients, only "isolette isolation" was adopted, and nurses were advised to observe careful handwashing technique. However, on March 16, the epidemic of NEC was recognized and additional prophylactic measures were adopted; these included confinement of all NEC patients to one room and of contacts to another room, and the placement of all new admissions in a third room. The contacts were patients who had been cared for by the same nurse or who were in the same room as the four patients with NEC. All patients were in isolettes, and their nurses were required to wear gowns and gloves. Consequently, in eight of the 18 contacts, obvious NEC developed, whereas the other ten contacts remained asymptomatic.

Our intermediate and intensive care unit consists of two rooms with a total bed capacity of 14 patients. When needed (as during the epidemic), a third room can be arranged to provide intensive care therapy. The nursing personnel are confined to one room, and within each room a nurse is responsible for two intensive care patients or three intermediate care newborns. However, during lunch hours the same nurse may provide care to other newborns within each room.

BACTERIOLOGIC FINDINGS

A search for a bacterial etiology of the enterocolitis began on March 16 by examination of stool and blood cultures from all four patients with NEC and stool cultures from all contacts. For those patients in whom signs of NEC developed later on, stool and blood cultures were repeated at the first sign of NEC, usually before the time of definite diagnosis. Unfortunately, a search for the source of the epidemic among nurses and house staff was not carried on.

Enterobacter cloacae type 3305573 was recovered as pure growth on the stool cultures from eight newborns with NEC (seven of these repeatedly); these cultures were positive early in the course of the disease or even before the appearance of the full clinical picture. The same *E cloacae* was also recovered from the blood cultures of two patients and at the postmortem examination of one. Thus, nine of the ten patients from whom adequate cultures were taken were infected with the same *E cloacae* in the early phase of their disease. A test for viruses was negative on the stool culture and at the electron microscopic examination of stools from four patients.

Among the initial 18 contacts identified on March 16, eight subsequently acquired a definite NEC; of these, six patients showed pure growth of *E cloacae* in their stool cultures, whereas two others (patients 7 and 10) died before adequate cultures were obtained. Among other contacts, four (4/10) had the same *E cloacae* in their stools but failed to show pure growth; *E cloacae* was mixed with two other enterobacteria (*Esch coli, Klebsiella*

and/or *Proteus mirabilis*). These patients were considered colonized but not infected; they had no sign of NEC, and aside from isolation, no specific therapy was required. These contacts who did not have NEC were not different from subjects with NEC in regard to gestational age (34.3 weeks), birth weight (1,795 g), early clinical course and incidence of early intravenous antibiotic therapy, umbilical catheter placement, and human-milk feeding.

After the epidemic period (the first week of May), all 15 patients in the NICU (12 new admissions and three patients of the epidemic) had a stool culture taken to ascertain the absence of endemic infection with *E cloacae* type 3305573 in the unit. All cultures were negative for *E cloacae*, but the usual mixed flora were found in 12 premature infants (*Esch coli*, *P mirabilis*,and *Serratia marcescens*) and no pathogens were found in the remaining three.

COMMENT

The clinical, radiological, and pathological features of NEC in the patients of this epidemic are similar to those reported in epidemics associated with other bacteria[2-5] or without known pathogens.[1,6] The role of *E cloacae* type 3305573 is not clear in this epidemic of NEC, but some arguments would favor a GI tract infection as the initial event in the pathogenesis of this disease in our predisposed population of premature newborns. First, the time course of events suggests an infectious epidemic. The first patient proven to have the incriminated *E cloacae* along with NEC during January might have been the source of the dissemination of the bacteria since only isolette isolation was recommended. Then, two weeks later, a cluster of NEC cases occurred, presumably following dissemination of the infectious agent to other newborns. A second argument relies on the type and the timing of the pure growth of *E cloacae* type 3305573 in the stools of patients with NEC. Eight of nine patients from whom adequate stool cultures were taken showed positive cultures very early in the course of NEC. Moreover, in six patients (2, 3, 4, 5, 6, and 12) the stool specimens showed pure growth of *E cloacae* before we could make a clinical and/or radiological diagnosis. A third argument is related to the pathogenicity of this bacterium, which was capable of inducing plurisystemic disease in our premature patients as demonstrated by septicemia in two patients and by diffuse infection at postmortem examination. Finally, as reported extensively by others in instances of nonepidemic NEC,[9] no clinical differences could be found in our patients in whom NEC developed and those in whom it did not. The only difference identified was the presence of *E cloacae* type 3305573.

Whether the enteric infection identified in our patients early in the course of NEC was an opportunistic infection occurring on a damaged intestinal mucosa remains unknown, but it appears likely that *E cloacae* type 3305573 was involved as an initial event in the development of NEC. This is consistent with other epidemics of NEC, particularly those occurring during a nosocomial infection with *C butyricum*,[5] *Salmonella*,[4] *Esch coli*,[2] and probably with *Klebsiella*.[3] All of these epidemics, as well as ours, were associated with an outbreak of a nosocomial infection involving bacteria that were proven not to be endemic in each of the NICUs, and all epidemics ceased with implementation of infection control measures. Reports of three other clusters of NEC failed, however, to identify a specific bacterium in association with the disease.[1,6,7] Additional reports of epidemiological data on clusters of NEC are needed to confirm the impression that some nosocomial infections can induce an epidemic of NEC in a predisposed population.

Nonproprietary Names and Trademarks of Drugs

Ampicillin trihydrate—*Amcill, Penbritin, Polycillin, Principen.*

Gentamicin sulfate—*Garamycin, Genoptic.*

References

1. Virnig NL, Reynolds JW: Epidemiological aspects of neonatal necrotizing enterocolitis. *Am J Dis Child* 128:186-190, 1974.
2. Speer ME, Taber LH, Yow MD, et al: Fulminant neonatal sepsis and necrotizing associated with a 'nonenteropathogenic' strain of *Escherichia coli*. *J Pediatr* 89:91-95, 1976.
3. Hill HR, Hunt CE, Matsen JM: Nosocomial colonization with *Klebsiella* type 26 in neonatal ICU associated with an outbreak of sepsis, meningitis, and NEC. *J Pediatr* 85:415-419, 1974.
4. Stein H, Beck J, Solomon A, et al: Gastroenteritis with necrotizing enterocolitis in premature babies. *Br Med J* 2:616-619, 1972.
5. Howard FM, Flynn DM, Bradley JM, et al: Outbreak of necrotizing enterocolitis caused by *Clostridium butyricum*. *Lancet* 2:1099-1102, 1977.
6. Guinan M, Schaberg D, Bruhn FW, et al: Epidemic occurrence of neonatal necrotizing enterocolitis. *Am J Dis Child* 133:594-597, 1979.
7. Book LS, Overall JC, Herbst JJ, et al: Clustering of necrotizing enterocolitis: Interruption by infection-control measures. *N Engl J Med* 297:984-986, 1977.
8. Bell MJ, Ternberg JL, Feigin RD, et al: Neonatal necrotizing enterocolitis: Therapeutic decision based upon clinical staging. *Ann Surg* 187:1-7, 1978.
9. Stoll BJ, Kanto WP, Glass RI, et al: Epidemiology of necrotizing enterocolitis: A case control study. *J Pediatr* 96:447-451, 1980.

Radiological Case of the Month

Chakib Bennani-Smires, MD, Jocyline Medina, MD (*Contributors*); Lionel W. Young, MD (*Section Editor*)

A 3,200-g male infant was delivered by cesarean section because of fetal distress after an uneventful 38-week gestation. On the second day of life, fever and diarrhea developed. At 2 weeks of age, because of his failure to tolerate oral feedings, persistent diarrhea, and dehydration, total parenteral hyperalimentation therapy was started. A complete blood cell count showed a hypochromic, normocytic anemia. Results of a stool examination, an upper gastrointestinal series, and barium enema examinations were normal. A biopsy of the small bowel showed flattening of the mucosa consistent with chronic intractable diarrhea. By 5 months of age, he weighed 5,100 g and was pale but alert, nourished almost continuously by parenteral hyperalimentation. Diarrhea was persistent and without a definite cause. On roentgenographic examination of the chest, subperiosteal new bone of the diaphyses of the humeri was noted, and a roentgenogram of the lower limbs was obtained (Fig 1). Although hypochromic anemia persisted, serum calcium and phosphorus levels were normal. A follow-up roentgenogram was obtained one month later (Fig 2).

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Figure 1.

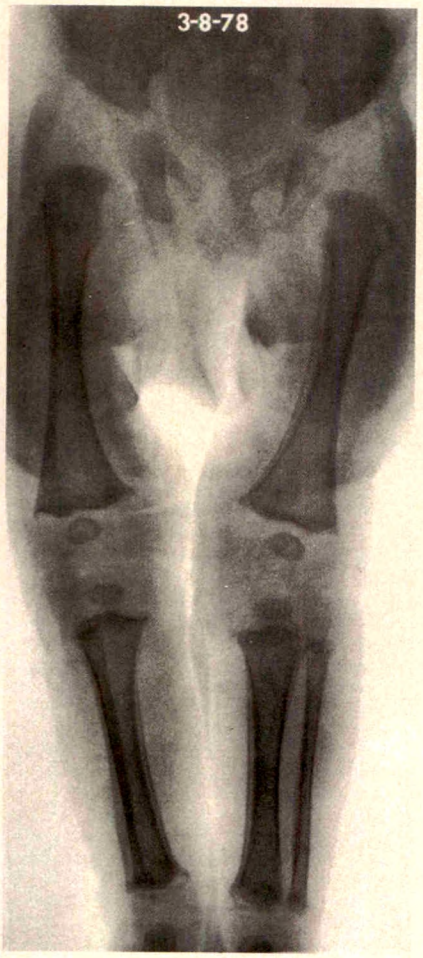
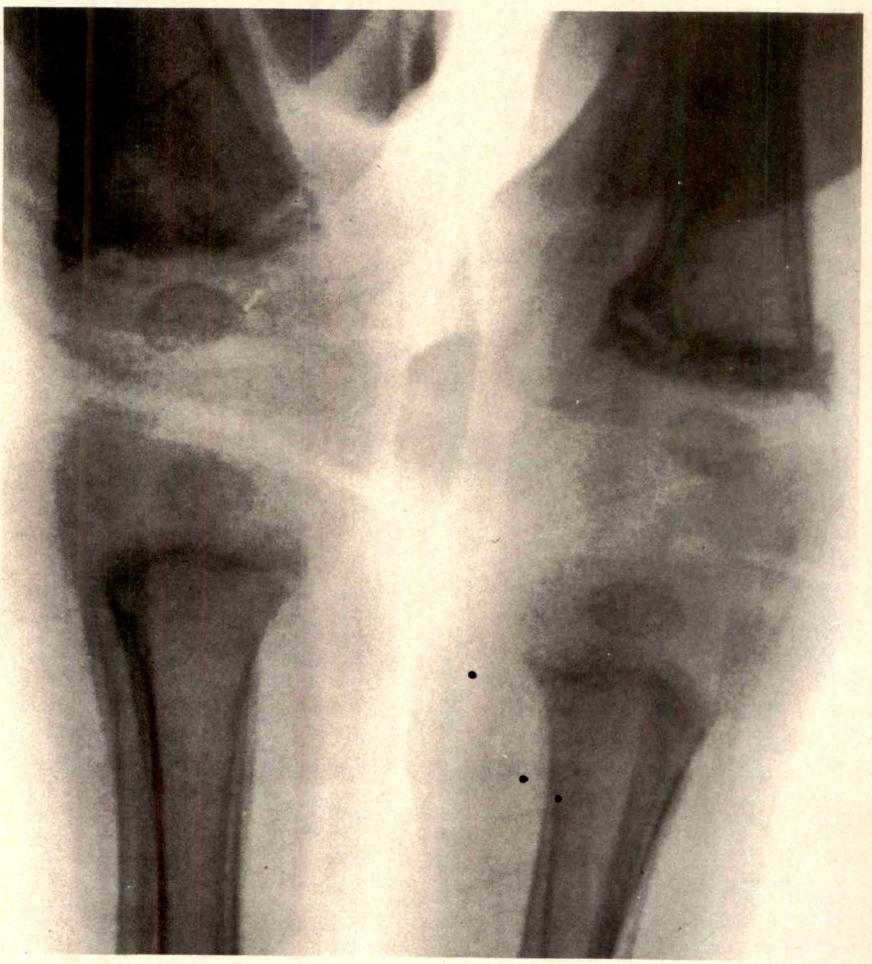


Figure 2.



Infantile Nutritional Copper Deficiency

Fig 1.—Anteroposterior view of lower limbs; marked osteoporosis and subperiosteal new bone are present in long bones and ilia. Metaphyses have wavy and irregular outline. Distal femoral and tibial metaphyseal infractions are present. Note bucket-handle deformities of distal metaphyses of tibiae.

Fig 2.—One month after initiation of copper therapy, subperiosteal new bone is again apparent, and new bone healing of metaphyseal infractions is evident.

Fig 3.—Subperiosteal new bone formation along long-bone shafts is less apparent (remodeling). Metaphyseal infractions are completely healed, and line of residual sclerosis in each metaphysis is present.

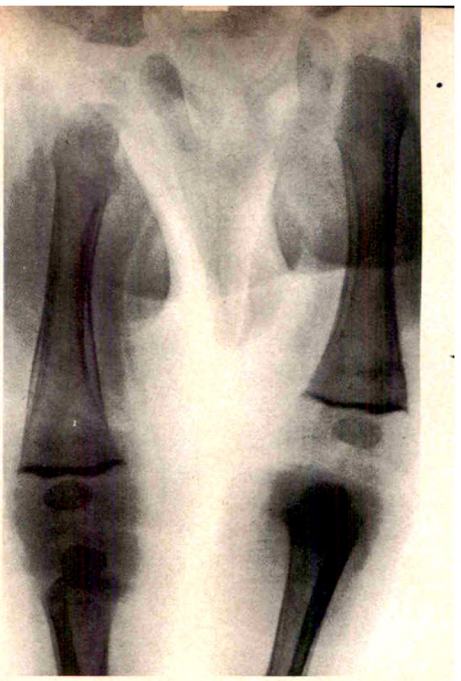


Figure 3.

Metaphyseal infractions of limb bones and subperiosteal new bone formation might occur in child abuse, but usually not bilaterally and symmetrically; neither would this be likely in an infant hospitalized since birth. Rickets would be unlikely because the blood levels of calcium and phosphorus were normal. Moreover, vitamin D in daily requirement doses was regularly given to our patient. Scurvy might be considered, but daily requirement levels of ascorbic acid were included in the parenteral feedings, and the roentgenographic changes are not typical for scurvy. A luetic origin is excluded because the serologic tests for syphilis in both parents were negative.

Corresponding long-bone roentgenographic changes were also present in the upper limbs, there being similar metaphyseal change in the proximal humeral metaphyses, although the distal metaphyses of the ulnae and radii appeared normal. The ribs showed rachitic-like cupping and splaying of their sternal ends.

Copper deficiency is especially consistent with the findings and symptoms in this infant who had received total parenteral nutrition since birth. Moreover, the serum level of ceruloplasmin was 0.6 mg/dL (normal, 17 to 28 mg/dL). The serum copper level was 7 μg/dL (normal, 60 to 190 μg/dL). After 21 days of copper therapy, the serum ceruloplasmin level was 14.5 mg/dL and the serum copper level was 71 μg/dL. Three months later, roentgenographic examination of the limbs showed conspicuous diaphyseal subperiosteal new bone remodeling and remodeling of the involved metaphyses, highlighted by a residual line of metaphyseal sclerosis (Fig 3).

Nutritional copper deficiency is rare. Usually the full-term infant has large reserves of copper in his liver. Case reports of infantile copper deficiency have been made in malnourished infants with chronic intestinal malabsorption,[1] in very small infants with pronounced liver damage,[2-4] and in infants and adults receiving prolonged total parenteral nutrition.[5,6] Normally, copper stores in the infant are sufficient for the first six months of life. The peak incidence of deficiency is at about 8 months of age.

The most important features of nutritional copper deficiency in infants are as follows: (1) the presence of a sideroblastic anemia with vacuolation of erythroid and myeloid bone marrow cells and iron deposition in the vacuoles and in some mitochondria[2]; (2) the coexistence of neutropenia, especially segmentopenia; (3) morphological findings of depigmentation of skin and hair and distended blood vessels due to changes in the elastin of the vessel walls; and (4) functional CNS deficits, including hypotonia and psychomotor retardation. The roentgenographic findings in nutritional copper deficiency are (1) long-bone osteoporosis, (2) cupping, flaring, and fractures of the metaphyses, (3) periosteal new bone, and (4) calcifications of the soft tissue.

The anemia is resistant to iron therapy in the absence of copper. The biochemical basis for the long-bone changes is the formation of an abnormal collagen with reduced structural integrity due to a decrease in the cross-links that normally form aldehyde groups and to a copper-dependent reaction along the polypeptide chains.[2,5]

Although this patient showed healing of the skeletal lesions, verifying the effectiveness of copper replacement therapy, the infant died at 9 months of age of severe sepsis and metabolic acidosis.

References

1. Cordano A, Graham GG: Copper deficiency complicating severe chronic intestinal malabsorption. *Pediatrics* 1966;38:596-606.
2. Ashkenazi A, Levin S, Djaldetti M, et al: The syndrome of neonatal copper deficiency. *Pediatrics* 1973;52:525-533.
3. Seely JR, Humphrey GB, Matter BJ: Copper deficiency in a premature infant fed on iron-fortified formula. *N Engl J Med* 1972;286:109-110.
4. Griscom NT, Craig JN, Neuhauser EBD: Systemic bone disease developing in small premature infants. *Pediatrics* 1971;48:883-895.
5. Heller RM, Kirschner SG, O'Neill TA Jr, et al: Skeletal changes of copper deficiency in infants receiving prolonged total parenteral nutrition. *J Pediatr* 1978;92:947-950.
6. Karpel JT, Peden VH: Copper deficiency in long-term parenteral nutrition. *J Pediatr* 1972;80:32-36.

Review

Vitamin E and the Neonate

Richard A. Ehrenkranz, MD

In 1922, Evans and Bishop[1] demonstrated the existence of a fat-soluble dietary factor that was required for reproduction in rats. Animals deficient in this factor, which was designated vitamin E,[2] ovulated and conceived normally, but fetal death and resorption occurred at some time during gestation.[3] Evans and his associates[4] isolated the vitamin from wheat germ oil in 1936 and proposed the name "α-tocopherol" from the Greek *tokos*, a noun meaning childbirth, and *phero*, a verb meaning to bear. The suffix, *-ol*, was added to indicate that the substance was an alcohol. Although eight different tocopherols with vitamin E activity have been shown to occur naturally, α-tocopherol (Fig 1) is considered to be the most important, since it possesses the greatest biological activity and comprises about 90% of the total tocopherols present in animal tissues.[5] The standard unit of vitamin E activity is DL-α-tocopheryl acetate, 1 mg being equal to 1 IU. Table 1 compares the activity of different α-tocopherol compounds.[5]

Vitamin E has been extensively investigated during the past several decades. The signs and symptoms of vitamin E deficiency in animals have been thoroughly reviewed[5,6] and include effects on the reproductive, muscular, cardiovascular, and hematopoietic systems. Although clinical correlations to these pathologic manifestations have been sought, vitamin E deficiency does not readily occur in adult humans owing to the resistance of their tissue stores to depletion and to its wide distribution in foods.[7,8] However, human vitamin E deficiency has been described in association with malabsorption syndromes of various origins and in neonates, especially premature neonates.[5-7] After discussing the mode of action of vitamin E, this communication will review vitamin E status in the perinatal period and the factors underlying the development of vitamin E-deficiency anemia in the neonate. The recommended dietary vitamin E requirements for the neonate will then be discussed with respect to the interrelationship of vitamin E, polyunsaturated fatty acids (PUFAs), and iron; and finally, the therapeutic importance of vitamin E in the neonatal period will be reviewed.

MECHANISM OF VITAMIN E ACTION

The precise mode of action of vitamin E has not been demonstrated; however, it is thought to function as a lipid antioxidant, diminishing the peroxidation of polyunsaturated lipids by scavenging free radicals generated during the univalent reduction of molecular oxygen[9] and during the normal activity of oxidative enzymes.[10] Lipid peroxidation is the oxidative deterioration of polyunsaturated lipids.[11,12] It involves the reaction of highly reactive intermediates of oxidative metabolism and lipid and results in the formation of semistable lipid peroxides.[11,12] Kinetic experiments by Gruger and Tappel[13] suggest that vitamin E inhibits peroxidation of membrane lipid by acting as a reducing agent and providing protons directly to free radicals to form water. In addition, vitamin E may interrupt the chain reactions associated with lipid peroxidation by scavenging lipid peroxides.[11,12] Scavenging reactions with methyl[14] and alkyl[15] radicals have been demonstrated.

Lucy[16] has also proposed that vitamin E is an important structural component of biological membranes, interacting with membrane phospholipids such that membranes containing relatively high levels of PUFAs would also require large amounts of vitamin E to ensure structural stability. His studies[16] with molecular models suggest that the methyl side groups of the vitamin E core may be linked to membrane phospholipids by fitting within the double-bond structure of linoleic, linolenic, and arachidonic acid residues. Inhibition of lipid peroxidation by vitamin E has been shown to correlate with its binding to complexes of unsaturated lipids and membrane structural proteins,[17] providing evidence that membrane-associated vitamin E accounted for the antioxidant influence.

The mechanisms of vitamin E action just discussed are based on in

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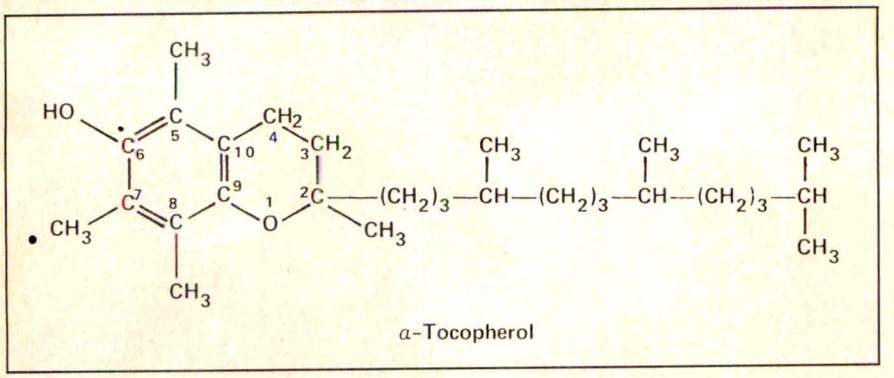

Fig 1.—Chemical structure of α-tocopherol.

Table 1.—Activity of Vitamin E Compounds

Compound	Content, mg/IU
DL-α-tocopheryl acetate	1.00
DL-α-tocopherol	0.91
DL-α-tocopheryl acid succinate	1.12
D-α-tocopheryl acetate	0.74
D-α-tocopherol	0.67
D-α-tocopheryl acid succinate	0.83

vitro studies. However, during the past several years, a number of investigators have reported in vivo evidence of vitamin E's antioxidant influence. Administration of carbon tetrachloride to mice[18] and rats[19] induced in vivo lipid peroxidation that was accompanied by the expiration of ethane, which could be diminished by pretreatment with vitamin E. Hafeman and Hoekstra[20] demonstrated that spontaneous in vivo lipid peroxidation, monitored by analysis of expired air for the presence of ethane, occurred in vitamin E- and selenium-deficient rats. Dillard and his colleagues have also correlated pentane expiration with in vivo lipid peroxidation in vitamin E-deficient rats[21] and in rats receiving various levels of dietary vitamin E, selenium, and PUFAs.[22] Figure 2 illustrates the reactions in which ethane evolves during the decomposition of linolenate hydroperoxide and pentane during the decomposition of linoleate or arachidonate hydroperoxide.[23] Pentane expiration was found to be directly related to the linoleic acid content of the diet[22] and inversely related to the dietary vitamin E concentration.[22-24] Dietary selenium decreased pentane production in vitamin E-deficient rats receiving a diet high in linoleic acid, but that effect was related to the activity of blood glutathione peroxidase, a selenoenzyme, which did not increase as the dietary selenium content was raised above the recommended level.[22]

Although Tappel[11,12] has stated that vitamin E is "the major biological antioxidant," endogenous antioxidant protection is provided by a number of other dietary components, including selenium, sulfur amino acids, and vitamin C.[11,12] Optimum tissue levels of these biologic antioxidants should result in adequate protection against oxidant and lipid peroxidative damage. The interrelationships between these substances, particularly selenium and vitamin E,[26] is complex and will not be discussed in any further detail in this report.

VITAMIN E STATUS IN THE PERINATAL PERIOD

Dju et al[26] measured the total body stores of vitamin E in human fetuses and neonates who died within nine days of birth. Twenty-two fetuses between 2 and 6 months of gestational age had an average of 3.1 mg of total tocopherols per kilogram of body weight compared with 5.6 mg of total tocopherols per kilogram of body weight in a 3,570-g full-term stillborn infant and an estimated 70 mg/kg of body weight in an adult. A linear relationship between total lipid or body weight and total tocopherol content of the fetuses was noted. Since adipose tissue was found to contain the greatest concentrations of tocopherols and since the amount of adipose tissue increases from less than 1% of body weight during the first two trimesters to approximately 16% of body weight at term,[27] Dju et al[26] stated that tocopherol body stores were low in the fetus and only slightly higher in premature and term infants.

A number of studies[28-35] have determined blood vitamin E levels in newborn infants and their mothers and have consistently noted that maternal levels at delivery or in the immediate postpartum period were higher than neonatal levels. Mean maternal levels ranged from 0.92 to 2.53 mg/dL compared with mean levels ranging from 0.24 to 0.61 mg/dL in the newborn (Table 2), with no significant difference in the vitamin E levels of premature and term infants.[29-31,35,36] Since the normal adult blood level of vitamin E is 1.05 mg/dL with a 2-SD range of 0.5 to 1.6 mg/dL,[7] these findings suggest that vitamin E levels are generally elevated during pregnancy and that the neonate may be considered chemically deficient in vitamin E. In addition, these data are consistent with the low fetal and neonatal body stores of vitamin E noted above.[26] Since the ratio of maternal to neonatal blood levels ranged from 2.6 to 5.7:1 (Table 2), the data also indicate that transfer of vitamin E from the mother to the fetus is limited. Leonard et al[31] noted a significant linear correlation between maternal blood levels of vitamin E and corresponding cord blood levels, finding that infants born to mothers with vitamin E levels less than 0.7 mg/dL had significantly lower vitamin E levels than infants born to mothers with vitamin E levels greater than 0.7 mg/dL. Mino and Nishino[32] confirmed that correlation and reported that, although supplementary vitamin E administration to women during the weeks prior to their delivery raised both the maternal and cord blood levels of vitamin E significantly, the levels in cord blood increased an average of only 0.11 mg/dL compared with an increase of 0.82 mg/dL in maternal blood (Table 2).

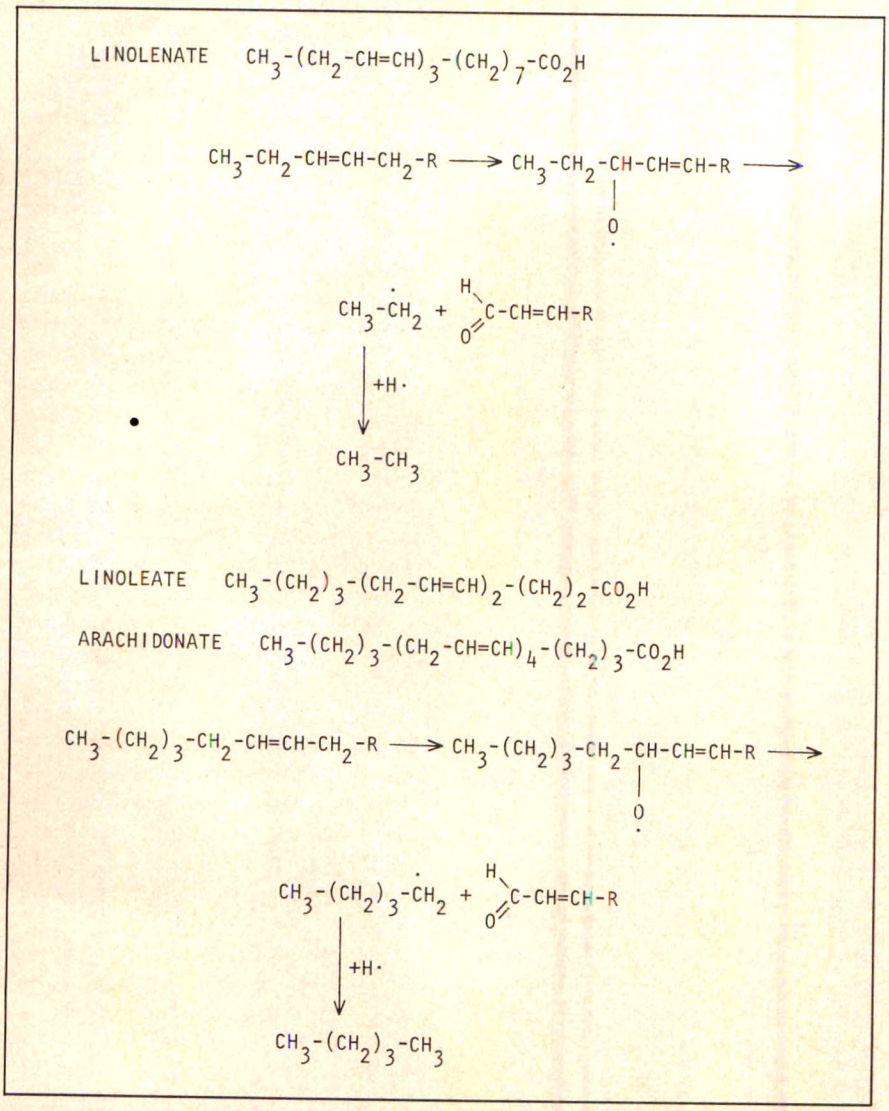

Fig 2.—Evolution of hydrocarbon gases during lipid peroxidation. Ethane evolves from decomposition of alkoxy radical of linolenate and pentane from alkoxy radical of linoleate and arachidonate (adapted from Dumelin and Tappel[23]).

A HISTORICAL PERSPECTIVE OF VITAMIN E DEFICIENCY ANEMIA

Although most neonates were found to be chemically vitamin E deficient at birth, several studies reported that term breast-fed infants increased their blood vitamin E levels to the adult range quickly, while term and premature infants fed artificial milk formulas continued to have low levels for months.[29,30,36] Wright et al[29] suggested that the greater vitamin E content of human milk as compared with artificial milk formulas accounted for this difference. In addition, although a number of investigators[30,37-39] had demonstrated that the increased RBC hemolysis measured with the hydrogen peroxide hemolysis test correlated with the presence of chemical vitamin E deficiency, a clinical vitamin E deficiency syndrome was not described until 1966. At that time, Hassan et al[40] reported the association of edema, especially of the legs, labia or scrotum, and eyelids, restlessness, watery nasal discharge, noisy and occasionally distressful or tachypneic respirations, skin lesions, and hematologic abnormalities with low vitamin E levels in premature infants. During the first six weeks of life, these infants had blood vitamin E levels that remained or fell below 0.45 mg/dL, increased erythrocyte sensitivity to hydrogen peroxide hemolysis, thrombocytosis, and peripheral blood smears that demonstrated characteristic morphologic abnormalities, specifically clumping of platelets, pronounced anisocytosis and poikilocytosis, and RBC fragments. Hassan and his co-workers[40] also noted that the edema, skin lesions, and hematologic abnormalities disappeared quickly following the administration of vitamin E and were not observed in infants fed the same diets supplemented with vitamin E. Since the affected infants had received formulas with a high PUFA content, a low vitamin E content, and vitamin E to PUFA (E:PUFA) ratios of 0.19 or 0.37 (refers to a ratio of the milligrams of dietary D-α-tocopherol to grams of dietary PUFA), the investigators suggested that the diet consumed by those infants had played an etiologic role in the development of this syndrome.

The relationship between the dietary content of PUFAs and the requirement for vitamin E had been the subject of several investigations[41-43] prior to the report of Hassan et al.[40] Essentially these and other studies had demonstrated that the requirement for vitamin E increased as the dietary content of PUFAs increased. After evaluating the average diet in the United States in 1960, Harris and Embree[43] proposed 0.6 as the "critical" dietary E:PUFA ratio. They suggested that diets with E:PUFA ratios greater than 0.6 generally protected against the development of chemical vitamin E deficiency. However, diets with ratios less than 0.6 were likely to contain an inadequate amount of vitamin E and would tend to permit the development of vitamin E deficiency. Therefore, since newborn infants, especially premature infants, have limited body stores of vitamin E at birth,[26] the findings[29,30,36,40] that they remained chemically vitamin E deficient and/or became increasingly deficient while being fed artificial milk diets with low E:PUFA ratios are understandable.

The report by Hassan et al[40] of a clinical syndrome associated with vitamin E deficiency was quickly con-

Table 2.—Blood Vitamin E Levels Reported in Mothers and Their Neonates

Mean Maternal Plasma or Serum Vitamin E, mg/dL	Mean Neonatal Plasma or Serum Vitamin E, mg/dL	Ratio of Maternal to Neonatal Vitamin E Levels	Source
1.70*	0.34*	5.7:1.0	Straumfjord and Quaife[28]
1.92†	0.38*	5.1:1.0	Wright et al[29]
1.32‡	0.24‡	5.5:1.0	Nitowsky et al[30]
0.92*	0.24*	3.9:1.0	Leonard et al[31]
1.71*	0.41*	4.2:1.0	Mino and Nishino[32]
2.53*§	0.52*	4.9:1.0	Mino and Nishino[32]
1.60*	0.61*	2.6:1.0	Tateno and Ohshima[33]
1.20*	0.30*	4.0:1.0	Baker et al[34]
2.10*‖	0.42*	5.0:1.0	Hågå and Lunde[35]

*Blood samples obtained at delivery (cord blood samples).
†Blood samples obtained two days postpartum postnatally.
‡Blood samples obtained one day postpartum postnatally.
§Women took supplementary vitamin E acetate (600 mg/day).
‖Maternal level estimated from graphic data.

firmed. Oski and Barness[44] described the development of hemolytic anemia in chemically vitamin E-deficient premature infants aged 6 to 10 weeks who had been fed proprietary formulas. The anemia was characterized by marked reticulocytosis, pyknocytosis, and other abnormal RBC forms and by shortened RBC survival times. Administration of vitamin E to affected infants resulted in a prompt increase in the hemoglobin level and a fall in the reticulocyte count. Daily vitamin E supplements beginning on the third day of life prevented or markedly decreased the severity of the hemolytic anemia. Then, Ritchie et al[45] reported that widespread edema, hemolytic anemia, reticulocytosis, and thrombocytosis accompanied vitamin E deficiency in seven premature infants aged 4 to 8 weeks, who, as above, had also received commercial formulas. Again, these abnormalities were corrected with vitamin E therapy.

Following the publication of these reports, a number of controlled studies[46-53] have investigated the interrelationships between vitamin E, diet, and hematologic indices in the neonate. The association of vitamin E deficiency and hemolytic anemia and the ability to prevent their development with daily vitamin E supplements have been supported by some investigators[46-51] but not by others.[52,53] Chadd and Fraser[46] showed that although hemoglobin levels were higher at 8 to 10 weeks of age in infants whose diets were supplemented daily with 15 mg of vitamin E from birth, the finding was only significant in term infants. However, Jansson et al[51] found the opposite effect, noting that daily supplements with 15 mg of vitamin E from 10 days of age only produced a significant increase in hemoglobin concentration at 8 to 10 weeks of age in premature infants and not in term infants. Melhorn and Gross[47] evaluated infants less than 36 weeks of gestational age receiving a standard commercial formula and found that, at 6 to 10 weeks of age, infants who had been supplemented with 25 IU of vitamin E per day from the eighth to the 42nd day of life had significantly higher mean hemoglobin concentrations and lower reticulocyte counts and erythrocyte sensitivity to hydrogen peroxide than infants whose diets were not supplemented. They also noted that the daily administration of medicinal amounts of elemental iron (approximately 10 mg/kg/day) from the 15th to the 42nd day of life exaggerated the hemolytic process in infants not receiving vitamin E supplements. In addition, some iron-fortified formulas have been found to promote the development of vitamin E-deficiency anemia.[49-50] Although Lo et al[48] did not begin vitamin E supplements (10 mg/day) until about 40 days of age when signs of hemolysis first appeared, they demonstrated a significant hematologic improvement after two to three weeks of treatment. Although their data only confirmed that vitamin E deficiency anemia responded to vitamin E administration, they suggested that premature infants receive a daily supplement of 10 mg of vitamin E.

Conversely, Hashim and Asfour[52] reported that although term infants who remained vitamin E deficient while being fed a diet with an E:PUFA ratio of 0.19 had hematologic changes during the first month of life consistent with those abnormalities seen in premature infants with vitamin E deficiency hemolytic anemia, a severe hemolytic anemia did not develop. Furthermore, a spontaneous increase in hemoglobin concentrations at a rate comparable to infants who were fed a vitamin E-supplemented diet or who were breast fed was noted. In addition, while attempting to evaluate the interrelationships between vitamin E and linoleic acid in premature infants, Panos et al[53] demonstrated that vitamin E supplementation (10 to 25 mg/day) was unable to prevent the fall in hemoglobin concentration at 5 to 7 weeks of age and that it did not effect RBC survival as measured by the chromium 51 labeling technique.

It is evident from this brief review of these reports that neonates, especially premature neonates, appear to be at risk for the development of a clinical syndrome resulting from vitamin E deficiency. This risk is related to many factors, including the following: maternal nutrition and blood level of vitamin E; the infant's birth weight, gestational age, and body stores of vitamin E at birth; dietary content of vitamin E, PUFAs, and iron; the E:PUFA ratio; and the ability of the infant to absorb vitamin E from his diet. In addition, although most investigators have demonstrated that daily vitamin E supplementation prevents vitamin E deficiency anemia with significant increases in hemoglobin concentrations between 6 and 10 weeks of age, discrepancies exist in the results of these studies. Reasons for those discrepancies include differences in the composition of the formulas, iron intakes, the dose and preparation of vitamin E, and the duration of vitamin E supplementation. Bell[54] performed a critical analysis of these

controlled studies that had been designed to detect vitamin E effects on the RBC and/or to evaluate whether supplemental vitamin E could prevent the development of hemolytic anemia, and stated that the findings were conflicting, gave somewhat equivocal results, and demonstrated hematologic manifestations that were of limited clinical value. Since the interrelationships between vitamin E, iron, and PUFAs have been one of the more controversial issues in neonatal nutrition, they will be discussed in more depth after a brief review of vitamin E absorption in the neonate.

ABSORPTION OF VITAMIN E

Bieri and Farrell[7] have recently reviewed the data from human and animal studies in this area. Esterified forms of vitamin E are almost completely hydrolyzed prior to absorption. Bile is essential for its absorption, and the predominant route of absorption is via gastrointestinal lymphatics. Approximately 45% of a dose of vitamin E is absorbed into the lymph as unchanged α-tocopherol, whereas degraded metabolites in portal venous blood and in feces account for most of the remainder of the dose. Vitamin E enters the bloodstream from the lymph. It does not appear to have a specific lipoprotein carrier, and circulating vitamin E is primarily associated with the low-density lipoproteins in man. Although most tissues take up vitamin E rapidly and establish a concentration that is proportional to the logarithm of the blood concentration, adipose tissue continually accumulates vitamin E.[7] Machlin et al[55] recently reported that guinea pigs fed a vitamin E-deficient diet for two to four months mobilized vitamin E stores quickly from liver and slower from heart and muscle but did not deplete adipose tissue stores. They suggested that the rate of release of vitamin E from adipose tissue was not sufficient to maintain adequate blood vitamin E levels or to prevent signs of vitamin E deficiency.

As apparent in the above discussion, the absorption of vitamin E and of other fat-soluble vitamins is related to the ability to digest and absorb dietary fats, an ability that is limited in all neonates.[56] Although premature infants absorb fat less efficiently than term infants, the percent absorption increases postnatally during the early weeks of life.[56] In addition, human milk fat is better absorbed than cow's milk fat and unsaturated fatty acids are absorbed better than saturated ones.[56,57] Thus, the finding in previously noted studies that blood vitamin E concentrations rose rapidly in term breast-fed infants, but tended to remain low for several months in term and premature infants fed artificial milk-based formulas,[29,30,36] could be accounted for not only by the greater vitamin E content of human milk compared with formulas,[29] but also by the neonate's ability to absorb dietary fats.

Although Filer et al[58] demonstrated that premature infants absorbed an oral dose of 20 mg/kg of α-tocopherol or α-tocopheryl esters as well as did full-term infants, Melhorn and Gross,[59] found a relationship between gestational age and the ability to absorb vitamin E. With the use of a modification of the vitamin E tolerance index method described by Filer and associates,[58] these investigators determined vitamin E absorption curves in premature infants at 3 weeks of age after a single oral dose of 25 mg/kg of α-tocopheryl acetate and calculated the tolerance index with the following formula:

$$(T_s - T_B) \times 100/\alpha\text{-}T$$

where T_s is the serum tocopherol value at eight hours, T_B is the baseline serum tocopherol value, and α-T is the amount of α-tocopherol administered in milligrams per kilogram of body weight. Figure 3 graphically represents their data and reveals that intestinal absorption of vitamin E as measured by the vitamin E tolerance index increases with gestational maturity. In addition, vitamin E tolerance studies performed at 3, 6, and 10 weeks of life on six infants born with birth weights between 1,000 and 1,500 g and gestational ages between 28 and 32 weeks demonstrated a progressive improvement in the ability to absorb vitamin E with increase in postnatal age. Thus, this increase with postnatal age occurs as the premature infant is increasing his ability to absorb fats. These workers also demonstrated that although 3-week-old premature infants absorbed a water-soluble preparation of vitamin E (D-α-tocopheryl polyethylene glycol 1,000-succinate [TPGS]) significantly better than the fat-soluble preparation (D-α-tocopheryl acetate), 3-day-old term infants absorbed both preparations equally, as well as markedly better than the 3-week-old premature infants.[49] Recently, Bell et al[60] reported that premature infants less than 1 week old who weighed less than 1,500 g at birth absorbed a dose of 25 IU of either DL-α-tocopherol or DL-α-tocopheryl acetate equally well and that an adequate blood vitamin E level could be maintained in those infants with a daily dose of 25 IU of DL-α-tocopherol.

Melhorn and Gross[59] also found that mixing elemental iron (ferrous sulfate) with vitamin E (α-tocopheryl acetate) decreased the vitamin E tolerance index considerably, and thus suggested that oral administration of iron might interfere with the intestinal absorption of vitamin E. This finding was consistent with their previous data,[47] which demonstrated that daily administration of medicinal amounts of iron exaggerated the vitamin E deficiency anemia in premature infants not receiving vitamin E supplements. However, premature infants did absorb vitamin E better from a formula that was fortified with elemental iron (15.7 mg/L) and contained 10.0 IU of the water-soluble preparation of vitamin E (TPGS) and 6.6 IU of the fat-soluble preparation (D-α-tocopheryl acetate) than from a formula that was also iron-fortified (13.7 mg of elemental iron per liter), but contained only 13.5 IU of the fat-soluble preparation.[49]

Since Tantibhedhyangkul and Hashim[61] reported that total fat absorption was significantly improved in premature infants fed formulas containing medium-chain triglycerides (MCTs, fatty acids containing eight to 12 carbon atoms in chains), some formulas specifically designed for premature infants have included MCTs as a significant percentage of their total fat content. Although intestinal

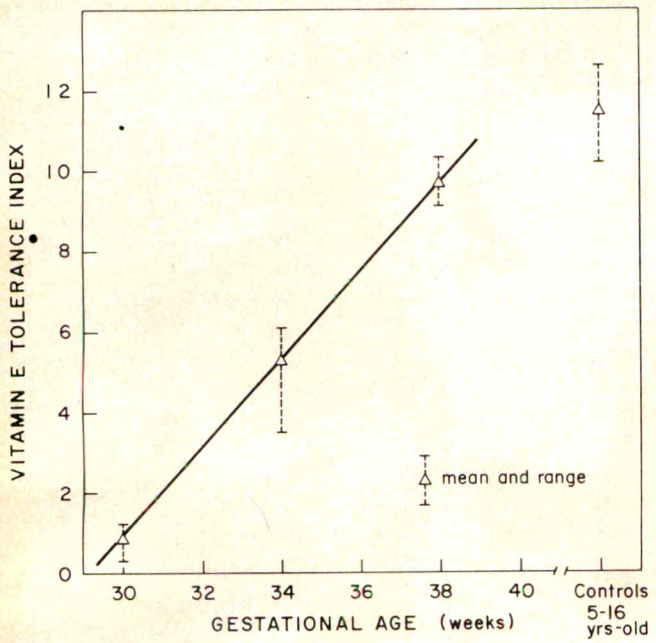

Fig 3.—Relationship between vitamin E tolerance index and gestational age. Tolerance index was determined in 3-week-old premature infants in following gestational age categories: 28 to 32 weeks, 32 to 36 weeks, and 36 to 40 weeks, and in healthy control children (adapted from Melhorn and Gross[59]).

absorption of vitamin E (D-α-tocopherol) in rats was enhanced by solubilization in MCTs as compared with long-chain triglycerides (LCTs, fatty acids containing 12 or more carbon atoms in chains),[62] Williams and Oski[63] recently reported that blood vitamin E levels in 6-week-old premature infants fed a formula containing 50% MCT and 50% LCT were not significantly different from vitamin E levels in similar infants fed a formula containing fats consisting completely of LCTs. However, since both of these formulas were fortified with iron, it is possible that the iron may have had a limiting effect on vitamin E absorption.

RATIO OF VITAMIN E TO POLYUNSATURATED FATTY ACID

As indicated in the discussion of vitamin E's mechanism of action, the requirement for vitamin E is related to the PUFA content of tissue lipids,[16] which in turn is influenced by the PUFA content of dietary lipid.[64-66] Although modification of tissue lipid PUFA concentration by changing the dietary content of PUFAs is quite complex,[64-66] increasing the dietary PUFA intake has generally been shown to increase the vitamin E requirement.[41-43] In addition, since the high PUFA content of many fats and oils is associated with a high total tocopherol content, although not necessarily with α-tocopherol content, diets including those foodstuffs may contain sufficient vitamin E activity to meet most of the increased requirements. As noted previously, Harris and Embree[43] proposed the use of an E:PUFA ratio of 0.6 as a guide to evaluate the adequacy of dietary vitamin E. However, they clearly stated that "experience has shown the impossibility of making flat rules for predicting the requirement of any nutrient without taking into account the rest of the diet, the environment, species, age or sex." Other investigators[7] have found that diets providing an E:PUFA ratio of 0.4 to 0.5 can produce an adequate vitamin E status in man. Witting[65] discussed the limitations of the recommendation of an E:PUFA ratio of 0.6,[43] and noted that although the vitamin E requirement is related to tissue PUFA content, tissue PUFA content might bear little relation to the dietary PUFA level, and thus, a 0.6 E:PUFA ratio is not applicable to all dietary regimens.

As with other tissues, the fatty acid composition of erythrocyte membranes is related to the fatty acid composition of the diet and has been shown to change readily with alterations in the dietary fatty acid content.[42,64,67,68] Hassan et al[40] and Hashim and Asfour[52] have demonstrated that feeding diets that were rich in linoleic acid to neonates resulted in an increase in the percentage of linoleic acid in erythrocyte lipids, the magnitude of that increase depending on the linoleic acid content of the formula. These investigators[40,52] also noted that the erythrocyte sensitivity to hydrogen peroxide hemolysis was highest at a time when the erythrocyte linoleic acid content was high and the blood vitamin E concentration was low. Since the diets given to these infants were also low in vitamin E (E:PUFA = 0.19 or 0.37), it was suggested that the increased erythrocyte susceptibility to peroxidation was related to insufficient antioxidant protection of membrane PUFAs and therefore that formulas with low E:PUFA ratios would predispose to the development of vitamin E deficiency anemia. In a recent study with premature infants weighing less than 1,500 g at birth, Williams et al[50] extended this observation by examining the effect of varying the dietary content of linoleic acid and iron while keeping the amount of vitamin E constant. They concluded that although formulas that contained adequate E:PUFA ratios could be fortified with iron, iron fortification of formulas with inadequate E:PUFA ratios increased the likelihood that vitamin E deficiency anemia would occur.

Table 3.—Composition of Human Milk and Some Current Proprietary Formulas

	Mature Human Milk[57]	Enfamil Premature Formula (Whey Protein)*	Enfamil 20*	Similac LBW*	Similac 20*	SMA*
Protein, g/dL	1.1	2.4	1.5	2.2	1.6	1.5
Fat, g/dL	4.5	4.1	3.7	4.5	3.6	3.6
Fatty acids shorter than C_{12}, %	2	43	3	53	6	6
Fatty acids C_{12} and longer, %	98	57	97	47	94	94
Polyunsaturated fatty acids, %	9	22	49	16	25	14
Carbohydrate, g/dL	6.8	8.9	7.0	8.5	7.2	7.2
Vitamin E, IU/dL†	0.27	1.6	1.3	1.8	1.5	1.0
Ratio of vitamin E to polyunsaturated fatty acids‡	0.4	1.2	0.5	1.7	1.1	1.3
Iron, mg/dL	0.10	0.13	0.15 (1.3)§	0.30	Trace (1.2)§	1.30
Calories, kcal/dL	67	81	67	81	67	67

*From appropriate product handbooks.
†Vitamin E as DL-α-tocopheryl acetate.
‡Milligrams of D-α-tocopherol per gram of polyunsaturated fatty acid; milligrams of D-α-tocopherol calculated from the international units of vitamin E contained in the formula as follows: milligrams of D-α-tocopherol per deciliter equals 0.67 mg/IU (international units of vitamin E per deciliter).
§Number in parenthesis is amount contained in iron-fortified formulation.

MEETING THE VITAMIN E REQUIREMENT OF THE NEONATE

On the basis of the reports[40,44,45] that vitamin E-deficiency anemia developed in premature infants who were receiving commercial formulas with high PUFA and low vitamin E contents, manufacturers of proprietary formulas increased the vitamin E content of their formulas to compensate for the use of fats with high percentages of PUFAs and to attain an adequate E:PUFA ratio. Although minimum dietary requirements for vitamin E have not been established, recommendations have been made by the American Academy of Pediatrics Committee on Nutrition.[69,70] The committee recommended that formulas designed for full-term infants contain a minimum of 0.3 IU of vitamin E per 100 kcal and at least 0.7 IU of vitamin E per gram of linoleic acid.[69] After consideration of the special needs of the premature infant, they recommended that formulas designed for premature infants provide a minimum of 0.7 IU of vitamin E per 100 kcal and at least 1.0 IU of vitamin E per gram of linoleic acid.[70] The use of a multivitamin preparation containing vitamin E was also suggested. Furthermore, since iron fortification of formulas high in PUFAs had been shown to increase the susceptibility of premature infants to vitamin E deficiency and hemolytic anemia,[49,50] the Committee on Nutrition[70] suggested that formulas for premature infants could provide either 0.1 mg or 1.5 mg of iron per 100 kcal and that if the higher level of iron was contained, sufficient vitamin E and a moderate level of PUFAs should be provided. Table 3 compares the composition of some of the current infant formulas with mature human milk.

In view of the Committee on Nutrition's[70] assessment of the nutritional needs of premature infants, most low-birth-weight premature infants in the Newborn Special Care Unit, Yale-New Haven (Conn) Hospital are fed an 81-kcal/dL (24-kcal/oz) commercial formula that contains a low level of iron and an appropriate proportion of vitamin E and PUFAs. The infants receive that formula until they weigh about 1,750 g, at which time they are switched to a 67-kcal/dL (20-kcal/oz) iron-fortified formula. In addition, each infant is given a daily supplement of a multivitamin preparation and an oral vitamin E preparation during their hospitalization. We have found that a daily oral dose of 50 IU of vitamin E (Aquasol E) for infants weighing less than 1,000 g and 25 IU for infants over 1,000 g usually maintains vitamin E blood levels within the normal adult range. Infants with cystic fibrosis, short gut syndrome, and other causes of chronic fat malabsorption receive at least 100 IU/day, which is continued following hospital discharge.

Although the composition of the present infant formulas appears to satisfy the recommendations of the Committee on Nutrition with respect to the interrelationships of vitamin E, PUFAs, and iron,[69,70] neonates who cannot be given enteral feedings and who require prolonged parenteral alimentation may remain chemically vitamin E deficient for long periods. Farrell[71] reported that the administration of parenteral fluids containing 1 IU of vitamin E per deciliter and providing 1 IU of vitamin E per kilogram per day took several days to correct vitamin E deficiency. We have studied serum vitamin E levels in two infants with short gut syndrome who received total parenteral alimentation containing 0.25 IU of vitamin E per deciliter and observed chemical vitamin E deficiency throughout the two- to three-month period of total parenteral alimentation (unpublished data). In addition, the effect of intravenous lipid emulsions on neonatal vitamin E requirements is not known. Although an analysis[71] of one proprietary lipid emulsion (Intralipid) demonstrated approximately 25 μg of total tocopherols per gram of lipid, γ-tocopherol, with low vitamin E activity, account for about 90% of that amount, while α-tocopherol account for only about 10%. Since lipid emulsions are rich in PUFAs, their use may predispose to vitamin E deficiency.

THERAPEUTIC IMPORTANCE OF VITAMIN E

The role of dietary vitamin E in preventing the development of vita-

min E-deficiency and hemolytic anemias in neonates has been reviewed previously and discussed in relation to the PUFA and iron content of the diet. Hemolytic anemia generally does not develop in infants with low blood levels of vitamin E unless they are receiving a diet that is rich in PUFAs, inadequate in vitamin E, and fortified with iron. Since most commercial infant formulas satisfy the recommendations of the Committee on Nutrition,[69,70] dietary-induced, vitamin E-deficiency hemolytic anemia does not occur frequently.

However, since vitamin E deficiency is associated with shortened RBC survival times,[44] several investigators have examined the effect of early vitamin E supplementation on the development of neonatal hyperbilirubinemia. Abrams et al[72] administered orally 100 mg of vitamin E (DL-α-tocopheryl acetate) daily from birth and, although plasma vitamin E levels were significantly increased, no significant effect on plasma bilirubin or hemoglobin concentration was noted during the first week of life. Conversely, Gross[73] recently reported that intramuscular (IM) administration of a total dose of 50 mg/kg of DL-α-tocopherol during days 1 to 3 of life resulted in a significant decrease in serum bilirubin concentration and in duration of phototherapy during the first week of life for infants with birth weights less than or equal to 1,500 g. This effect was less pronounced in infants with birth weights more than 1,500 g. Gross[73] suggested that this finding was consistent with a reduction in the accelerated RBC destruction characteristic of premature infants.

In addition to protecting erythrocytes, vitamin E appears to play a role in platelet and polymorphonuclear leukocyte (PMN) function and in immune response. Lake et al[74] demonstrated that the thrombocytosis seen in infants with vitamin E deficiency was associated with marked platelet hyperaggregability and that vitamin E supplementation resulted in a significant decrease in the platelet count and a normalization of platelet aggregation. However, Stuart and Oski[75] have also shown that vitamin E excess resulted in in vitro inhibition of platelet prostaglandin synthesis and aggregation. Recently, Boxer and coworkers[76] reported that although PMNs obtained from vitamin E-deficient rats had decreased chemotoxic and phagocytic activity, presumably secondary to oxidative damage, vitamin E-repleted PMNs had decreased bactericidal potency. Tengerdy and associates have described a significantly increased humoral immune response, as measured by the antibody plaque-forming cell test or by hemagglutination, in chicks[77] and mice[78] fed vitamin E-enriched diets.

Although these physiologic effects of vitamin E are achievable with dietary supplementation, two pharmacologic uses of vitamin E in the neonate have been proposed. These therapies are based on the findings of a large number of animal experiments that have demonstrated that vitamin E-deficient animals had more oxygen-induced damage to the lungs, the RBC, and the CNS than animals receiving a control diet[79-82] and that vitamin E treatment of vitamin E-deficient rats decreased the oxygen-induced lung injury.[82] Since chemical vitamin E deficiency is common in most neonates, vitamin E administration should increase endogenous antioxidant protection and therefore might reduce the incidence of retrolental fibroplasia (RLF) and bronchopulmonary dysplasia (BPD), two complications of oxygen use in the neonate. Johnson et al[83] administered an IM water-miscible preparation of DL-α-tocopheryl acetate to infants with a birth weight less than or equal to 2,000 g or to infants who required oxygen therapy and suggested that vitamin E reduced the incidence, severity, and duration of the acute stages of RLF. A clinical trial by Curran and Cantolino[84] also suggested a beneficial effect of vitamin E treatment on the incidence of RLF, and Phelps and Rosenbaum[85] have noted that vitamin E significantly reduced acute oxygen-induced retinopathy in newborn kittens. Recently, I and my co-workers[86] reported the results of a preliminary study that suggested that the IM administration of a water-dispersible preparation of DL-α-tocopherol during the acute phase of therapy for respiratory distress syndrome modified the development of BPD. This finding is supported by studies in newborn rabbits that demonstrated that vitamin E decreased morphologic evidence of acute oxygen-induced pulmonary injury after 72 hours of 100% oxygen exposure.[87] Since these clinical studies have drawn conclusions from a small number of patients, the randomized double-blind studies now in progress by these and other investigators will clarify whether vitamin E can prevent the development of RLF and BPD. So far, preliminary results from some of the studies[88-90] evaluating the efficacy of vitamin E in preventing the development of BPD have not confirmed the initial report.[86] However, since each of these investigations has used inspiratory pressures during positive-pressure mechanical ventilation that were markedly lower than the inspiratory pressures reported by me and my associates,[86] and since such limitation of the inspiratory peak pressure has been shown to decrease the incidence of BPD,[91] a large number of patients will be required to determine whether treatment with vitamin E can further decrease the incidence and severity of BPD. Milner et al[92] have recently emphasized the need for sample sizes large enough to minimize β error and to permit demonstration of the effectiveness of vitamin E in reducing the incidence of RLF and BPD.

Finally, although no side effects of pharmacologic vitamin E treatment have been noted in the neonatal reports other than local reactions at the injection sites,[83,86] side effects of high-dose vitamin E therapy have been described in adults and animals. In human subjects, high-dose vitamin E therapy has been associated with numerous subjective complaints and creatinuria[93] and exacerbation of a warfarin-induced coagulopathy.[94] In animals, side effects have included impaired wound healing[95] and anti-inflammatory activity[96] in rats and hepatic abnormalities and death in kittens.[97]

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References

1. Evans HM, Bishop KS: On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science* 56:650-651, 1922.
2. Sure B: Dietary requirements for reproduction: II. The existence of a specific vitamin for reproduction. *J Biol Chem* 58:693-709, 1924.
3. Evans HM, Bishop KS: On the relationship between fertility and nutrition: II. The ovulation rhythm in the rat on inadequate nutritional regimes. *J Metab Res* 1:319-356, 1922.
4. Evans HM, Emerson OH, Emerson GA: The isolation from wheat germ oil of an alcohol, α-tocopherol, having properties of vitamin E. *J Biol Chem* 113:319-332, 1936.
5. Cohn VH: Fat-soluble vitamins: Vitamin K and vitamin E, in Goodman LS, Gilman A (ed): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co Inc, 1975, pp 1591-1600.
6. Horwitt MK: Vitamin E, in Goodhart RS, Shils ME (eds): *Modern Nutrition in Health and Disease: Dietotherapy*, ed 5. Philadelphia, Lea & Febiger, 1973, pp 175-185.
7. Bieri JG, Farrell PM: Vitamin E. *Vitam Horm* 34:31-75, 1976.
8. Bunnell RH, Keating J, Quaresimo A, et al: Alpha-tocopherol content of foods. *Am J Clin Nutr* 17:1-10, 1965.
9. Gerschman R: The biological effects of increased oxygen tension, in Schaefer KE (ed): *Man's Dependence on the Earthly Atmosphere*. New York, Macmillan Publishing Co Inc, 1962, pp 171-179.
10. McCay PB, Pfeifer PM, Stipe WH: Vitamin E protection of membrane lipids during electron transport functions. *Ann NY Acad Sci* 203:62-73, 1972.
11. Tappel AL: Vitamin E as the biological lipid antioxidant. *Vitam Horm* 20:493-510, 1962.
12. Tappel AL: Lipid peroxidation damage to cell components. *Fed Proc* 32:1870-1874, 1973.
13. Gruger EH Jr, Tappel AL: Reactions of biological antioxidants: I. FE(III)-catalyzed reactions of lipid hydroperoxides with α-tocopherol. *Lipids* 5:326-331, 1970.
14. Urano S, Matsuo M: A radical scavenging reaction of α-tocopherol with methyl radical. *Lipids* 11:380-383, 1976.
15. Urano S, Yamanoi S, Hattori Y, et al: Radical scavenging reactions of α-tocopherol: II. The reaction with some alkyl radicals. *Lipids* 12:105-108, 1977.
16. Lucy JA: Functional and structural aspects of biological membranes: A suggested structural role for vitamin E in the control of membrane permeability and stability. *Ann NY Acad Sci* 203:4-11, 1972.
17. Tinberg HM, Barber AA: Studies on vitamin E action: Peroxidation inhibition in structural protein-lipid micelle complexes derived from rat liver microsomal membranes. *J Nutr* 100:413-418, 1970.
18. Rieley CA, Cohen G, Lieberman M: Ethane evolution: A new index of lipid peroxidation. *Science* 183:208-210, 1974.
19. Hafeman DG, Hoekstra WG: Protection against carbon tetrachloride-induced lipid peroxidation in the rat by dietary vitamin E, selenium, and methionine as measured by ethane evolution. *J Nutr* 107:656-665, 1977.
20. Hafeman DG, Hoekstra WG: Lipid peroxidation in vivo during vitamin E and selenium deficiency in the rat as monitored by ethane evolution. *J Nutr* 107:666-672, 1977.
21. Dillard CJ, Dumelin EE, Tappel AL: Effect of dietary vitamin E on expiration of pentane and ethane by the rat. *Lipids* 12:109-114, 1977.
22. Dillard CJ, Litov RE, Tappel AL: Effects of dietary vitamin E, selenium, and polyunsaturated fats on in vivo lipid peroxidation in the rat as measured by pentane production. *Lipids* 13:396-402, 1978.
23. Dumelin EE, Tappel AL: Hydrocarbon gases produced during in vitro peroxidation of polyunsaturated fatty acids and decomposition of preformed hydroperoxides. *Lipids* 12:894-900, 1977.
24. Downey JE, Irving DH, Tappel AL: Effects of dietary antioxidants on in vivo lipid peroxidation in the rat as measured by pentane production. *Lipids* 13:403-407, 1978.
25. Hoekstra WG: Biochemical function of selenium and its relation to vitamin E. *Fed Proc* 34:2083-2089, 1975.
26. Dju MY, Mason KE, Filer LJ Jr: Vitamin E (tocopherol) in human fetuses and placentae. *Etudes Néo-Natales* 1:49-60, 1952.
27. Widdowson EM, Spray CM: Chemical development in utero. *Arch Dis Child* 26:205-214, 1951.
28. Straumfjord JV, Quaife ML: Vitamin E levels in maternal and fetal blood plasma. *Proc Soc Exp Biol Med* 61:369-371, 1946.
29. Wright SW, Filer LJ Jr, Mason KE: Vitamin E blood levels in premature and full term infants. *Pediatrics* 7:386-393, 1951.
30. Nitowsky HM, Cornblath M, Gordon HH: Studies of tocopherol deficiency in infants and children: II. Plasma tocopherol and erythrocyte hemolysis in hydrogen peroxide. *Am J Dis Child* 92:164-174, 1956.
31. Leonard PJ, Doyle E, Hartington N: Levels of vitamin E in the plasma of newborn infants and of the mothers. *Am J Clin Nutr* 25:480-484, 1972.
32. Mino M, Nishino H: Fetal and maternal relationship in serum vitamin E level. *J Nutr Sci Vitaminol* 19:475-482, 1973.
33. Tateno M, Ohshima A: The relation between serum-vitamin E levels in the perinatal period and the birthweight of the neonate. *Acta Obstet Gynaec Jpn* 20:177-181, 1973.
34. Baker H, Frank O, Thomson AD, et al: Vitamin profile of 174 mothers and newborns at parturition. *Am J Clin Nutr* 28:56-65, 1975.
35. Hägä P, Lunde G: Selenium and vitamin E in cord blood from preterm and full term infants. *Acta Paediatr Scand* 67:735-739, 1978.
36. Moyer WJ: Vitamin E levels in term and premature newborn infants. *Pediatrics* 6:893-896, 1950.
37. Gordon HH, DeMetry JP: Hemolysis in hydrogen peroxide of erythrocytes of premature infants: Effect of alpha-tocopherol. *Proc Soc Exp Biol Med* 79:446-450, 1952.
38. György P, Cogan G, Rose CS: Availability of vitamin E in the newborn infant. *Proc Soc Exp Biol Med* 81:536-538, 1952.
39. Leonard PJ, Losowsky MS: Relationship between plasma vitamin E level and peroxide hemolysis test in human subjects. *Am J Clin Nutr* 20:795-798, 1967.
40. Hassan H, Hashim SA, Vanltallie TB, et al: Syndrome in premature infants associated with low plasma vitamin E levels and high polyunsaturated fatty acid diet. *Am J Clin Nutr* 19:147-157, 1966.
41. Mason KE, Filer LJ Jr: Interrelationships of dietary fat and tocopherols. *J Am Oil Chem Soc* 24:240-242, 1947.
42. Horwitt MK: Interrelations between vitamin E and polyunsaturated fatty acids in adult men. *Vitam Horm* 20:541-558, 1962.
43. Harris PL, Embree ND: Quantitative consideration of the effect of polyunsaturated fatty acid content of the diet upon the requirements for vitamin E. *Am J Clin Nutr* 13:385-392, 1963.
44. Oski FA, Barness LA: Vitamin E deficiency: A previously unrecognized cause of hemolytic anemia in the premature infant. *J Pediatr* 70:211-220, 1967.
45. Ritchie JH, Fish MB, McMasters V, et al: Edema and hemolytic anemia in premature infants: A vitamin E deficiency syndrome. *N Engl J Med* 279:1185-1190, 1968.
46. Chadd MA, Fraser AJ: A controlled trial of vitamin E therapy in infancy. *Int J Vitam Res* 40:610-616, 1970.
47. Melhorn DK, Gross S: Vitamin E-dependent anemia in the premature infant: I. Effects of large doses of medicinal iron. *J Pediatr* 79:569-580, 1971.
48. Lo SS, Frank D, Hitzig WH: Vitamin E and haemolytic anaemia in premature infants. *Arch Dis Child* 48:360-365, 1973.
49. Gross S, Melhorn DK: Vitamin E-dependent anemia in the premature infant: III. Comparative hemoglobin, vitamin E, and erythrocyte phospholipid responses following absorption of either water-soluble or fat-soluble d-alpha tocopheryl. *J Pediatr* 85:753-759, 1974.
50. Williams ML, Shott RJ, O'Neal PL, et al: Role of dietary iron and fat on vitamin E deficiency anemia of infancy. *N Engl J Med* 292:887-890, 1975.
51. Jansson L, Holmberg L, Nilsson B, et al: Vitamin E requirements of preterm infants. *Acta Paediatr Scand* 67:459-463, 1978.
52. Hashim SA, Asfour RJ: Tocopherol in infants fed diets rich in polyunsaturated fatty acids. *Am J Clin Nutr* 21:7-14, 1968.
53. Panos TC, Stinnett B, Zapata G, et al: Vitamin E and linoleic acid in the feeding of premature infants. *Am J Clin Nutr* 21:15-39, 1968.
54. Bell EF: Vitamin E in the premature infant, in Sunshine P (ed): *Feeding the Neonate < 1500 Grams-Nutrition and Beyond: Report of the 79th Ross Conference on Pediatric Research*. Columbus, Ohio, Ross Laboratories, to be published.
55. Machlin LJ, Keating J, Nelson J, et al: Availability of adipose tissue tocopherol in the guinea pig. *J Nutr* 109:105-109, 1979.
56. Avery GB, Fletcher AB: Nutrition, in Avery GB (ed): *Neonatology-Pathophysiology and Management of the Newborn*. Philadelphia, JB Lippincott Co, 1975, pp 839-897.
57. Fomon SJ: *Infant Nutrition*, ed 2. Philadelphia, WB Saunders Co, 1974.
58. Filer LJ Jr, Wright SW, Manning MP, et al: Absorption of α-tocopherol and tocopheryl esters by premature and full term infants and children in health and disease. *Pediatrics* 8:328-339, 1951.
59. Melhorn DK, Gross S: Vitamin E-dependent anemia in the premature infant: II. Relationships between gestational age and absorption of vitamin E. *J Pediatr* 79:581-588, 1971.
60. Bell EF, Brown EJ, Milner R, et al: Vitamin E absorption in small premature infants. *Pediatrics* 63:830-832, 1979.
61. Tantibhedhyangkul P, Hashim SA: Medium-chain triglyceride feeding in premature infants: Effects on fat and nitrogen absorption. *Pediatrics* 55:359-370, 1975.
62. Gallo-Torres HE, Ludorf J, Brin M: The effect of medium-chain triglycerides on the bioavailability of vitamin E. *Int J Vitam Nutr Res* 48:240-249, 1978.
63. Williams ML, Oski FA: Vitamin E status of infants fed formula containing medium-chain triglycerides. *J Pediatr* 96:70-72, 1980.
64. Witting LA: The role of polyunsaturated fatty acids in determining vitamin E requirements. *Ann NY Acad Sci* 203:192-198, 1972.

65. Witting LA: Recommended dietary allowance for vitamin E. *Am J Clin Nutr* 25:257-261, 1972.

66. Witting LA: Vitamin E-polyunsaturated lipid relationship in diet and tissues. *Am J Clin Nutr* 27:952-959, 1974.

67. Witting LA, Harvey CC, Century B, et al: Dietary alterations of fatty acids of erythrocytes and mitochondria of brain and liver. *J Lipid Res* 2:412-418, 1961.

68. Fitch CD, Dinning JS, Witting LA, et al: Influence of dietary fat on the fatty acid composition of monkey erythrocytes. *J Nutr* 75:409-413, 1961.

69. Committee on Nutrition, American Academy of Pediatrics: Commentary on breast-feeding and infant formulas, including proposed standards for formulas. *Pediatrics* 57:278-285, 1976.

70. Committee on Nutrition, American Academy of Pediatrics: Nutritional needs of low-birthweight infants. *Pediatrics* 60:519-530, 1977.

71. Farrell PM: Vitamin E deficiency in premature infants. *J Pediatr* 95:869-872, 1979.

72. Abrams BA, Gutteridge JMC, Stocks J, et al: Vitamin E in neonatal hyperbilirubinemia. *Arch Dis Child* 48:721-724, 1973.

73. Gross SJ: Vitamin E and neonatal bilirubinemia. *Pediatrics* 64:321-323, 1979.

74. Lake AM, Stuart MJ, Oski FA: Vitamin E deficiency and enhanced platelet function: Reversal following E supplementation. *J Pediatr* 90:722-725, 1977.

75. Stuart MJ, Oski FA: Vitamin E and platelet function. *Am J Pediatr Hematol/Oncol* 1:77-82, 1979.

76. Boxer LA, Harris RE, Baehner RL: Regulation of membrane peroxidation in health and disease. *Pediatrics* 64:713-718, 1979.

77. Tengerdy RP, Heinzerling RH: The effect of vitamin E on the immune response of hypoxic and normal chickens. *Ann NY Acad Sci* 203:177-180, 1972.

78. Tengerdy RP, Heinzerling RH, Brown GL, et al: Enhancement of the humoral immune response by vitamin E. *Int Arch Allergy* 44:221-232, 1973.

79. Kann HE Jr, Mengel CE, Smith W, et al: Oxygen toxicity and vitamin E. *Aerospace Med* 35:840-844, 1964.

80. Poland RL, Bollinger RO, Bozynski ME, et al: Effect of vitamin E deficiency on pulmonary oxygen toxicity, abstracted. *Pediatr Res* 11:577, 1977.

81. Taylor DW: Effects of vitamin E deficiency on oxygen toxicity in the rat. *J Physiol* 121:47p-48p, 1953.

82. Taylor DW: The effects of vitamin E and of methylene blue on the manifestations of oxygen poisoning in the rat. *J Physiol* 131:200-206, 1956.

83. Johnson L, Schaffer D, Boggs TR Jr: The premature infant, vitamin E deficiency and retrolental fibroplasia. *Am J Clin Nutr* 27:1158-1173, 1974.

84. Curran JS, Cantolino SJ: Vitamin E (injectable) administration in the prevention of retinopathy in prematurity: Evaluation with fluorescein angiography and fundus photography, abstracted. *Pediatr Res* 12:404, 1978.

85. Phelps DL, Rosenbaum AL: The role of tocopherol in oxygen-induced retinopathy: Kitten model. *Pediatrics* 59:998-1005, 1977.

86. Ehrenkranz RA, Bonta BW, Ablow RC, et al: Amelioration of bronchopulmonary dysplasia after vitamin E administration: A preliminary report. *N Engl J Med* 299:564-569, 1978.

87. Wender DF, Thulin GE, Smith GJW, et al: Vitamin E (E) affects lung morphologic response to hyperoxia, abstracted. *Pediatr Res* 14:653, 1980.

88. Ehrenkranz RA, Ablow RC, Warshaw JB: Prevention of bronchopulmonary dysplasia with vitamin E administration during the acute stages of respiratory distress syndrome. *J Pediatr* 95:873-878, 1979.

89. Abbasi S, Johnson L, Boggs T: Effect of vitamin E by infusion in sick small premature infants at risk for BPD, abstracted. *Pediatr Res* 14:638, 1980.

90. Saldanha RL, Cepeda EE, Poland RL: Effect of prophylactic vitamin E on the development of bronchopulmonary dysplasia in high-risk neonates, abstracted. *Pediatr Res* 14:650, 1980.

91. Taghizadeh A, Reynolds EOR: Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. *Am J Pathol* 82:241-264, 1976.

92. Milner R, Blanchette V, Ling E, et al: Vitamin E, sample size, and beta error, abstracted. *Pediatr Res* 14:606, 1980.

93. Hillman RW: Tocopherol excess in man: Creatinuria associated with prolonged ingestion. *Am J Clin Nutr* 5:597-600, 1957.

94. Corrigan JJ Jr: Coagulation problems relating to vitamin E. *Am J Pediatr Hematol/Oncol* 1:169-173, 1979.

95. Ehrlich HP, Tarver H, Hunt TK: Inhibitory effects of vitamin E on collagen synthesis and wound repair. *Ann Surg* 175:235-240, 1972.

96. Levy L: The antiinflammatory action of some compounds with antioxidant properties. *Inflammation* 1:333-345, 1976.

97. Phelps DL: Toxicity of pharmacologic parenteral doses of vitamin E in the neonatal kitten, abstracted. *Pediatr Res* 13:372, 1979.

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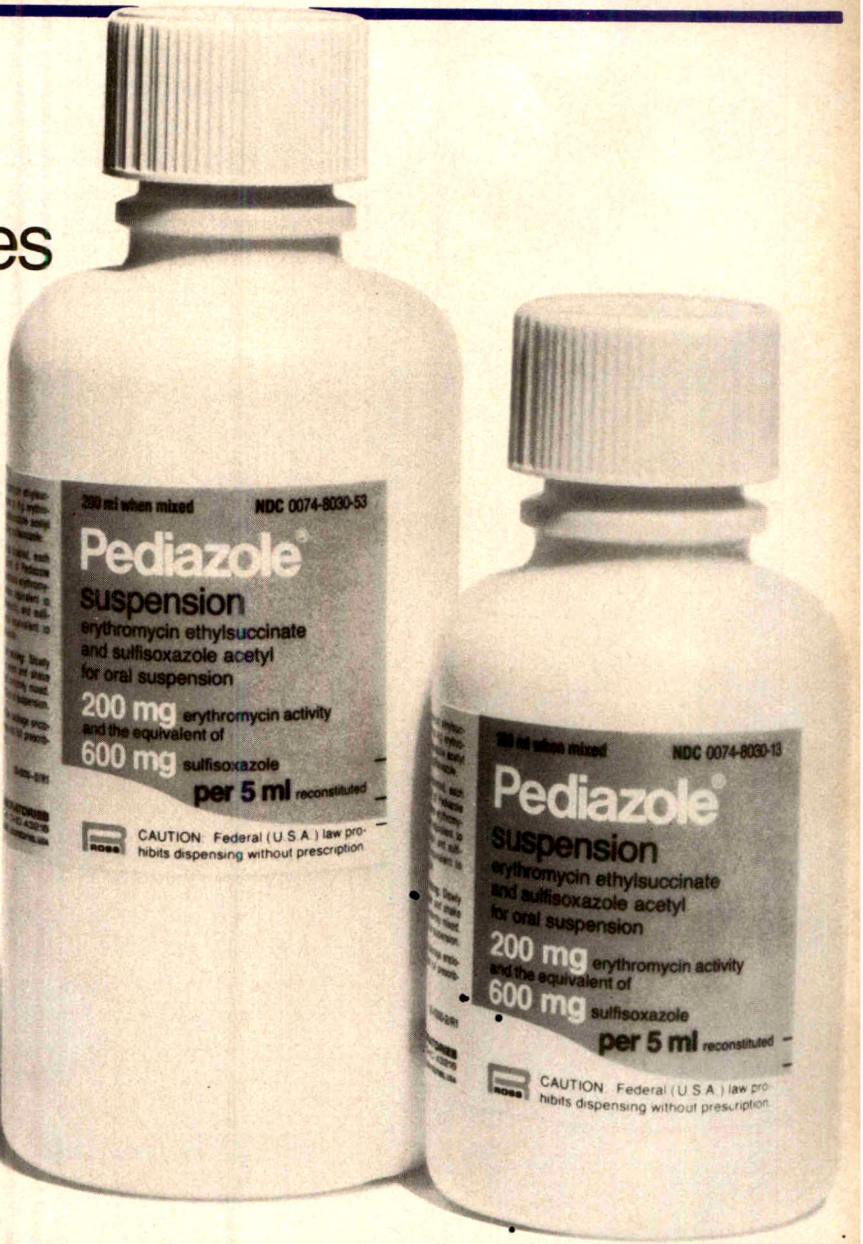

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Indications

Cyclacillin has less in vitro activity than other drugs in the ampicillin class and its use should be confined to these indications: Treatment of the following infections:

RESPIRATORY TRACT

Tonsillitis and pharyngitis caused by Group A beta-hemolytic streptococci

Bronchitis and pneumonia caused by *S. pneumoniae* (formerly *D. pneumoniae*)

Otitis media caused by *S. pneumoniae* (formerly *D. pneumoniae*) and *H. influenzae*

Acute exacerbation of chronic bronchitis caused by *H. influenzae**

*Though clinical improvement has been shown, bacteriologic cures cannot be expected in all patients with chronic respiratory disease due to *H. influenzae*.

SKIN AND SKIN STRUCTURES (integumentary) infections caused by Group A beta-hemolytic streptococci and staphylococci, non-penicillinase producers.

URINARY TRACT INFECTIONS caused by *E. coli* and *P. mirabilis*. (This drug should not be used in any *E. coli* and *P. mirabilis* infections other than urinary tract.)

NOTE: Perform cultures and susceptibility tests initially and during treatment to monitor effectiveness of therapy and susceptibility of bacteria. Therapy may be instituted prior to results of sensitivity testing.

Contraindications Contraindicated in individuals with history of an allergic reaction to penicillins.

Warnings Cyclacillin should only be prescribed for the indications listed herein.

Cyclacillin has less *in vitro* activity than other drugs of the ampicillin class. However, clinical trials demonstrated it is efficacious for recommended indications.

Serious and occasional fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin. Although anaphylaxis is more frequent following parenteral use, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. There are reports of patients with history of penicillin hypersensitivity reactions who experienced severe hypersensitivity reactions when treated with a cephalosporin. Before penicillin therapy, carefully inquire about previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and initiate appropriate therapy. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, I.V. steroids, airway management, including intubation, should also be administered as indicated.

Precautions Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

PREGNANCY: Pregnancy Category B. Reproduction studies performed in mice and rats at doses up to 10 times the human dose revealed no evidence of impaired fertility or harm to the fetus due to cyclacillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are, exercise caution when cyclacillin is given to a nursing woman.

Adverse Reactions Oral cyclacillin is generally well tolerated. As with other penicillins, untoward sensitivity reactions are likely, particularly in those who previously demonstrated penicillin hypersensitivity or with history of allergy, asthma, hay fever, or urticaria. Adverse reactions reported with cyclacillin: diarrhea (in approximately 1 out of 20 patients treated), nausea and vomiting (in approximately 1 in 50), and skin rash (in approximately 1 in 60). Isolated instances of headache, dizziness, abdominal pain, vaginitis, and urticaria have been reported. (See WARNINGS) Other less frequent adverse reactions which may occur and are reported with other penicillins are anemia, thrombocytopenia, thrombocytopenic purpura, leukopenia, neutropenia and eosinophilia. These reactions are usually reversible on discontinuation of therapy.

As with other semisynthetic penicillins, SGOT elevations have been reported.

As with antibiotic therapy generally, continue treatment at least 48 to 72 hours after patient becomes asymptomatic or until bacterial eradication is evidenced. In Group A beta-hemolytic streptococcal infections, at least 10 days' treatment is recommended to guard against risk of rheumatic fever or glomerulonephritis. In chronic urinary tract infection, frequent bacteriologic and clinical appraisal is necessary during therapy and possibly for several months after. Persistent infection may require treatment for several weeks.

Cyclacillin is not indicated in children under 2 months of age.

Patients with Renal Failure Cyclacillin may be safely administered to patients with reduced renal function. Due to prolonged serum half-life, patients with various degrees of renal impairment may require change in dosage level (see DOSAGE AND ADMINISTRATION in package insert).

Dosage (Give in equally spaced doses)

INFECTION	ADULTS	CHILDREN*
Respiratory Tract		
Tonsillitis & Pharyngitis	250 mg q.i.d.	body weight < 20 kg (44 lbs) 125 mg q.i.d. body weight > 20 kg (44 lbs) 250 mg q.i.d.
Bronchitis and Pneumonia		
Mild or Moderate Infections	250 mg q.i.d.	50 mg/kg/day q.i.d.
Chronic Infections	500 mg q.i.d.	100 mg/kg/day q.i.d.
Otitis Media	250 mg to 500 mg q.i.d.†	50 to 100 mg/kg/day†
Skin & Skin Structures	250 mg to 500 mg q.i.d.†	50 to 100 mg/kg/day†
Urinary Tract	500 mg q.i.d.	100 mg/kg/day

*Dosage should not result in a dose higher than that for adults.
†depending on severity

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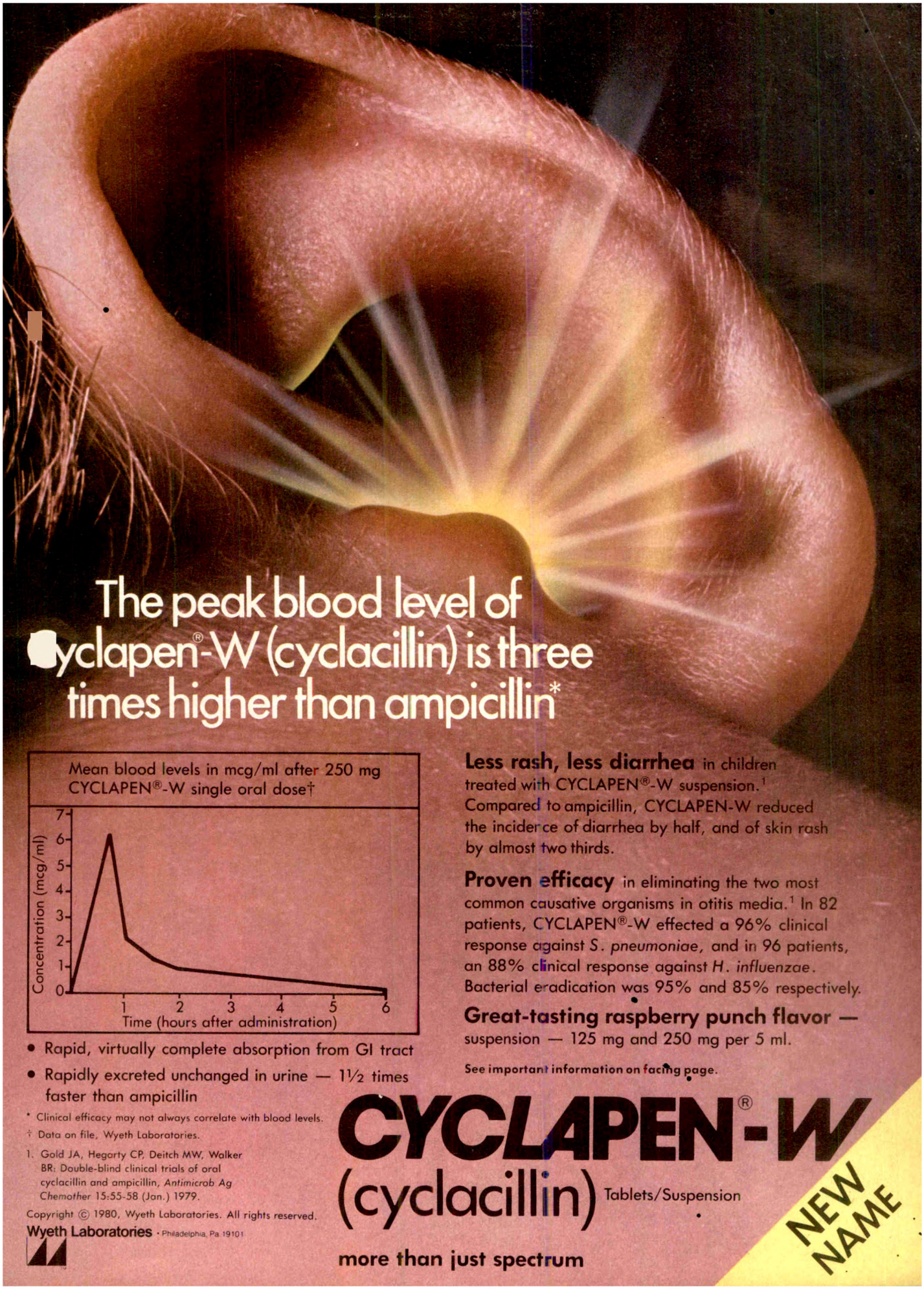

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1. Gold JA, Hegarty CP, Deitch MW, Walker BR: Double-blind clinical trials of oral cyclacillin and ampicillin, *Antimicrob Ag Chemother* 15:55-58 (Jan.) 1979.

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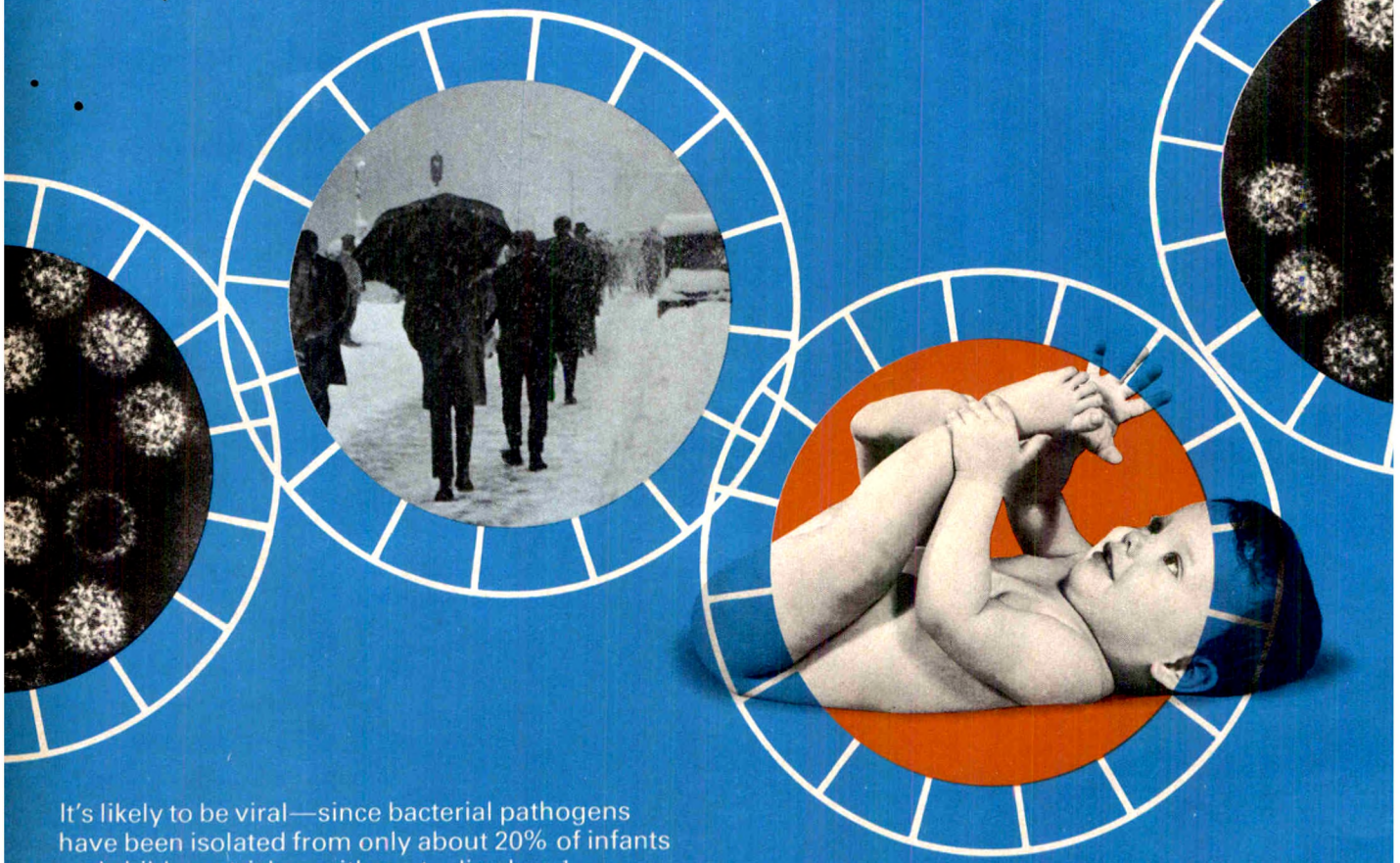

It's likely to be viral—since bacterial pathogens have been isolated from only about 20% of infants and children stricken with acute diarrhea.[1]

Diarrhea and subsequent dehydration are common symptoms of infectious gastroenteritis, a serious disease which is responsible for hospitalization of more than 300,000 children in the U.S. annually. Today it is believed that about half of those children suffer from a specific type of viral infection—rotavirus.[2]

Rotavirus infections, singled out as the most important cause of non-bacterial gastroenteritis among children, are most prevalent now, during the winter months.

Rapid diagnosis is important.

Rotavirus infections are highly contagious and fast spreading, especially in the hospital setting. In one study, 20% of 60 infants at risk on hospital admission developed diarrhea within 72 hours.[3] An early definitive diagnosis removes uncertainty, eliminates unnecessary antibiotic treatment, and permits a rational approach to isolation and epidemiological control.

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1. St. Geme J.W.: A new look at infectious gastroenteritis. West J. Med. 121: 456-461, 1974.
2. Hodes, H.L.: Viral Gastroenteritis. Am. J. Dis. Child. 131: 729-731, 1977.

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The Association of 'Prune Belly' With Turner's Syndrome

It has been postulated that fetal abdominal distention causes abdominal muscle deficiency, or "prune belly." Although urethral obstruction was proposed as the most common mechanism, other possible pathways were suggested, including fetal ascites secondary to impaired lymphatic development in cases of 45,X Turner's syndrome.[1] We describe two patients with Turner's syndrome and prune belly and call attention to additional cases in the European literature that further delineate this association.

Report of Cases.—CASE 1.—This female infant was 2.8 kg at birth after the uncomplicated term pregnancy, labor, and delivery of her gravida 2, para 3, 23-year-old mother. The father was 25 years old. Turner's syndrome was diagnosed neonatally. Long leg casts were required for genu recurvatum from the ages of 2 to 8 months. She has a mild to moderate conductive hearing loss. Her development is grossly normal. She has had one urinary tract infection.

The mother reported that an intravenous pyelogram (IVP) showed one kidney smaller than the other. Two karyotypes were 45,X, without evidence of mosaicism. Family medical history was unremarkable.

At 3 years of age, the girl's height was 82.5 cm (below the third percentile), weight, 10.4 kg, and head circumference, 47 cm (tenth percentile). The facies was triangular with relative hypertelorism, epicanthus, and micrognathia. Auricles were prominent and cup-shaped, with hypoplastic helices. Angles of the mouth were downturned, the palate was narrow and high, and the neck short with bilateral webbing. The chest was broad with widely spaced nipples, pectus carinatum, and a short sternum. No heart murmurs were heard. Abdominal examination showed absent external and internal oblique muscles. Musculus rectus abdominis appeared normal and the transversus abdominis was at least partially present. Genitalia were normal.

The dorsa of the hands and feet were puffy. The elbows showed decreased extension and cubitus valgus. There was bilateral genu recurvatum and metatarsus varus. The nails were narrow and hypoplastic, the hands short and wide. Flexion creases were normal on the right and bridged on the left. Dermatoglyphics showed eight ulnar loops and two whorls. Deep tendon reflexes were 3+ on the lower extremities, 2+ on the upper.

CASE 2. This female infant was 1.95 kg at birth after the term pregnancy of her 21-year-old, gravida 2, para 1 mother. Amniotic fluid was meconium stained. There was respiratory distress secondary to pneumomediastinum, left pneumothorax, and right pleural effusion needing repeated taps, and finally a right-sided chest tube for presumed chylothorax. There were episodes of apnea and bradycardia. After 11 days she had a cardiac arrest and could not be resuscitated.

Her head circumference was 30 cm (below the third percentile), her ears low-set, and her neck webbed. Abdominal muscles were absent. Labia minora were prominent. There was distal edema and generalized hypotonia.

An IVP showed delayed visualization of a small left kidney and a right megaloureter without obstructive renal changes. The karyotype was 45,X,22ps+ (22ps+ is a normal variant).

Previous Cases.—Previous cases of Turner's syndrome and prune belly have been noted. These include Smith's patient[3] (presumably the same infant described by Pagon et al[1]), and possibly the child pictured on page 324 of Moore's book.[4] Two reports in the foreign literature antedating chromosome analysis fit the clinical picture. Partial summaries follow.

At the age of 23 months, Benesova's patient[5] weighed 11 kg and was 79 cm tall. Speech was limited to single words, the muscle tone was normal, the ears were angulated, the nasal bridge was broad, the palpebral fissures were oblique, the neck was short with bilateral skin folds, and there was mild hypertelorism. The thorax was wide, barrel-like, and excavated distally. The abdominal wall was soft with palpable circular defects in the muscle wall bilaterally, cranially extending to the rib cage, caudally 2 cm below the umbilicus, medially to the rectus muscle edge, and laterally to the ventral axillary line. With crying, there was a mild bulging the size of a tangerine on the right and the size of a walnut on the left. There was edema of the dorsal arms, basal digits, and the dorsum and phalanges of the feet. There was a mild crural atrophy and a mild convergent strabismus.

The patient described by Jeune and Jacquot[6] was one month premature, weighed 3.0 kg at birth, and had a bronchoalveolar pneumonia at 14 days of age. The neck showed pterygium colli with cutis laxa. There was cutis laxa of the extremities and a lymphangiectatic edema of the right leg. There was aplasia of the left *jumeau interne* (translation uncertain) muscle, epicanthus, a gothic palate, and hypoplastic nipples, but no cubitus valgus or joint limitations. Isolated dextrocardia was noted. The abdominal musculature showed total aplasia. Cystography showed left ureterovesical reflux. She died of the lung disease after ten days.

Comment.—These cases support the concept of an etiologically distinct variant of prune belly syndrome in 45,X female infants. Urinary tract anomalies tended to be milder than those in typical male infants with the syndrome.[7] Similar findings are common in Turner's syndrome,[8] and their presence is probably coincidental rather than causative.

In these cases, Turner's syndrome was recognized early, and congenital stigmata were prominent. Probably the majority of XO female infants are diagnosed after the failure of menstruation,[9] and phenotypic manifestations are often mild.[8] The most obvious congenital findings are swellings of the dorsa of the hands and feet and webbing of the neck, all probably related to lymphatic abnormalities. The presence of such obvious findings in all known cases of prune belly, and the absence of karyotyped Turner's syndrome in females ascertained with abdominal muscle hypoplasia but without such stigmata,[2] suggest a role for the lymphatic abnormality, although whether this is direct or mediated through the production of ascites is uncertain.

The variability seen is of interest. In all cases, the rectus muscles were spared, suggesting a differential sen-

sitivity to pressure. In the male, variability may depend on the anatomy of the distended urinary tract rather than on underlying muscular vulnerability.

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1. Pagon RA, Smith DW, Shepard TH: Urethral obstruction malformation complex: A cause of abdominal muscle deficiency and the 'prune belly.' *J Pediatr* 1979;94:900-906.

2. Rabinowitz R, Schillinger JF: Prune belly syndrome in the female subject. *J Urol* 1977;118:454-456.

3. Smith DW: *Recognizable Patterns of Human Malformation*, ed 2. Philadelphia, WB Saunders Co, 1976, p 47.

4. Moore KL: *The Sex Chromatin*. Philadelphia, WB Saunders Co, 1966, p 324.

5. Benesova E: Syndrom Bonnevie-Ullrichov. *Pediatr Listy* 1949;6:258-259.

6. Jeune M, Jacquot F: Un cas de syndrome d'Ulrich avec aplasie de la musculature abdominale. *Pediatrie* 1952;7:792-794.

7. Warkany J: *Congenital Malformations: Notes and Comments*. Chicago, Year Book Medical Publishers, 1971, pp 1026-1029.

8. De Grouchy J, Turleau C: *Clinical Atlas of Human Chromosomes*. New York, John Wiley & Sons Inc, 1977, pp 225-234.

9. Neu RL, Gardner LI: Abnormalities of the sex chromosomes, in Gardner L (ed): *Endocrine and Genetic Diseases of Childhood and Adolescence*. Philadelphia, WB Saunders Co, 1975, pp 793-814.

Fetal Damage due to Aminopterin Ingestion: Follow-up at 17½ Years of Age

In 1962, a female infant was delivered at 39 weeks' gestation to a mother who had attempted to induce abortion by ingesting an unknown amount of aminopterin sodium between days 55 and 58, with profound toxic effects, including epistaxis, loss of hair, and ulcerations of the mouth and skin. Failing to abort and realizing the danger of her fetus, she demanded an abortion but was refused. Her toxic symptoms subsided before delivery. The status of the child has been reported at birth, at 33 months, and at 9 years of age.[1,2] This is an update on her amazing improvement at 17½ years of age.

The Patient.—At birth her weight was 1,750 g, and her appearance resembled an identically injured neonate described by Warkany et al[3] who had died at 24 hours of age. Our patient was not expected to live but improved after several days. Her globular skull was almost devoid of ossification except for a small area at the base; the orbita were poorly formed; the eyelids were everted; and the eyebrows were deficient and lacked pigmentation in the lateral half. Her hair was curiously backswept, as was that of the patient described by Warkany et al.[3] She had marked micrognathia and extraordinary foreshortening of her forearms and legs, and both radial heads were defective and subluxated.

At 4½ and at 9 years of age, there had been surprising improvement. Her linear growth and weight gain had been at about the 2.5 percentile. At 17½ years of age, she is a slender, short (150 cm) young adult, weighing 40.4 kg (her mother is similarly proportioned). She does not appear dwarfed. Her skull has ossified normally (circumference, 50 cm); the previous frontal bossing is no longer present, and the metopic suture is closed. Her hair is blonde and abundant, and the eyebrows are normally present but less pigmented on the outer half. Micrognathia is still marked; her teeth are crowded and protruding, but she is receiving skilled but difficult orthodontic care. Her orthodontist (Carl A. Kuhn, DDS), reports that her mandible, which usually grows very fast in infancy, has not kept pace with her extremities and it has been necessary to extract several teeth to accommodate her dentition to her jaw size. Her facial appearance is not unattractive. The black nevus below her mouth is unchanged. Her extremities are now normal in length, proportion, and mobility. Secondary sex characteristics and sexual development are normal; menstruation began at 11½ years of age and is normal.

This girl is a ward of the court and has had the advantage of care from devoted foster parents. Earlier in childhood, she was handicapped socially by her peculiar appearance but she now seems well adjusted and has many friends. Except for arithmetic, at which she is poor, she does acceptably well at school. Numerous psychometric studies at school have produced results within a normal but rather low range. She is not especially athletic but joins in normal physical activities involving running and throwing. She plays the organ acceptably. In short, this child who was so badly damaged at birth has gained to acceptably normal young-adult status.

Comment.—When this child was initially described she was believed to be the only survivor past neonatal life of this disastrous fetal damage. However, several similar patients have since been identified.[4-6] Two personal communications indicate cases so similar that a common etiology seems likely.

Apparently, all of the mothers of similarly involved children took aminopterin at about the same period in pregnancy and suffered similar side effects. The infants are so similarly affected that one could suspect the etiology in any others with similar defects. Uniformly, there have been abnormalities in skull development, facial defects, micrognathia, and often palatal defects, as well as maldevelopment of long bones with defects of linear growth and bony development. All the described adult survivors are remarkably similar. None has had defective mental capacity; some are even reported as being quite superior.[4]

It is unlikely that aminopterin will ever again be used as an abortifacient. Nevertheless, this inadvertent pharmacological experiment in teratogenesis might conceivably be repeated in the treatment of malignant neoplasms during pregnancy or other situations. The resemblances of the cases involved either in early infancy or in adult life are so similar that their encounter might suggest etiology from the same agent or a similar one. Growth and repair are quite similar phenomena. Many deformities present at birth from teratologic or genetic influences persist relentlessly in later years. It is amazing that such a profound degree of damage due to aminopterin could be overcome to a considerable extent during growth from birth to adulthood.

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1. Shaw EB, Steinbach HL: Aminopterin-induced fetal malformations: Survival of infant after attempted abortion. *Am J Dis Child* 115:477-482, 1968.

2. Shaw EB: Fetal damage due to maternal aminopterin ingestion: Follow-up at age 9 years. *Am J Dis Child* 124:93-94, 1972.

3. Warkany J, Beaudry PH, Hornstein S: Attempted abortion with aminopterin (4-aminopteroylglutamic acid): Malformations of the child. *Am J Dis Child* 97:274-281, 1959.

4. Reich EW, Cox RP, Becker MH, et al: Recognition in adult patients of malformations induced by folic acid antagonists. *Birth Defects* 14:139-160, 1978.

5. Meltzer HJ: Congenital anomalies due to attempted abortion with 4-aminopteroglutamic acid. *JAMA* 161:1253, 1956.

6. Brandner M, Nussle D: Foetopathie due à l'aminoptérine avec sténose congénitale de l'espace médullaire des os tubulaires ongs. *Ann Radiol* 12:705-710, 1969.

Severe Meningococcal Disease Caused by Serogroups X and Z

The minor serogroups of *Neisseria meningitidis* (X,Y, and Z-W135 and 29 E) were initially considered to be of low virulence and were thought to produce very mild clinical disease. However, since 1974, many reports have appeared in the literature that clearly document that severe meningococcal disease does occur with group Y and group W135.[1-7] To our knowledge, there have been no previous reports of severe meningococcal disease in children caused by serogroups X or Z. We report two such cases. One case is that of severe meningococcemia and meningitis with disseminated intravascular coagulation (DIC) caused by group X *N meningitidis* and one is that of fatal fulminant meningococcemia and meningitis with DIC caused by group Z *N meningitidis*.

Report of Cases.—CASE 1.—A 9-month-old infant was well until one day prior to admission, when she experienced fever, vomiting, and a rash. The child was seen at a local emergency room with a temperature of 40.5 °C. She was diagnosed as having an upper respiratory tract infection and sent home. The rash began to spread and the child was seen at another hospital and again sent home. By this time, the child was covered with "purple bruises" and was limp and very lethargic. The parents brought the child to the University of Mississippi Medical Center (UMC), Jackson.

On admission, the child was lethargic with extensive purpuric lesions on the face, trunk, and extremities. The temperature was 37.5 °C, the pulse rate was 200 beats per minute, the respiratory rate was 20/min, and the blood pressure (BP) was 100/60 mm Hg. The child's fingertips were cyanotic and cold.

Laboratory Data.—The CSF revealed 42 cells with 93% neutrophils. The CSF protein level was 17 mg/dL and the glucose level was 75 mg/dL. The CSF Gram's stain revealed Gram-negative diplococci. The WBC count was 12,400/cu mm. The coagulation studies revealed a platelet count of 310,000/cu mm, prothrombin time of 18 s with a control of 11 s, partial thromboplastin time of 60 s with a control of 35 s, and thrombin time of 15 s with a control of 14 s. Fibrin split products were positive in dilutions of 1:5 and 1:20. Blood and CSF cultures revealed N *meningitidis* group X.

The child was treated with aqueous penicillin G and also received steroids. Her hospital course was marked by extensive skin loss and autoamputation of the fingers of the right hand and the tips of the second, fourth, and fifth fingers of the left hand.

CASE 2.—A 2-year-old boy was well until two days prior to admission, when he experienced a cold manifested by rhinorrhea. One day prior to admission, he was irritable and had a low-grade fever, but continued his normal activity. Four hours prior to admission, when put to bed, he was noted to have one "red spot" beneath the left eye but was otherwise well. He was checked three hours later, and was noted to have a high fever and a generalized rash. He was brought to the UMC.

On admission, the child was unresponsive, with a BP of 70/0 mm Hg and temperature of 41.7 °C. There was an extensive purpuric rash. The child experienced generalized seizure activity. He was treated with hydrocortisone sodium succinate (Solu-Cortef), aqueous penicillin G, anticonvulsants, and an exchange transfusion. However, his condition deteriorated rapidly and he died within hours of admission.

Laboratory Data.—The WBC count was 5,500/cu mm with 2,200 neutrophils and 1,100 band forms. The CSF cell count was 1,260, with a predominance of neutrophils. The CSF protein level was 200 mg/dL and the glucose level was 6 mg/dL. Coagulation studies revealed a platelet count of 29,000/cu mm, prothrombin time of 22.3 s with a control of 12.3 s, and a partial thromboplastin time of 74.3 s with a control of 29.6 s. Fibrin split products were positive at dilutions of 1:5 and 1:20. Electrolyte values were normal. Cultures of CSF and blood were positive for *N meningitidis* Z.

Comment.—The clinical disease in these two patients was indistinguishable from that produced by the major serogroups of *N meningitidis*. In both patients, the disease was that of fulminant meningococcemia and meningitis with DIC. One child (case 1) suffered severe thromboembolic phenomena with infarction of the fingers on both hands. The other child (case 2) arrived in shock and died shortly after admission.

Serogroups X and Z must be added to the growing list of *N meningitidis* serogroups capable of producing severe clinical disease. It is reasonable to assume that any of the serogroups are potentially pathogenic for man.

The efficacy of group-specific meningococcal vaccination has been well documented.[8-11] The increasing frequency of serious illness caused by the minor serogroups may be of major importance if vaccination programs are to be effective in controlling epidemic disease. To broaden the potential protection afforded by meningococcal vaccination, a polyvalent vaccine that includes groups A, C, and Y has been developed and shown to be effective in clinical trials.[12] A polyvalent meningococcal vaccine affording protection against all serogroups is not yet available, but with the changing serogroups producing severe meningococcal disease, such a vaccine may become necessary if epidemic meningococcal disease is to be controlled.

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1. Risko JA, Hodges GR: *Neisseria meningitidis* serogroup Y: Incidence and description of clinical illness. *Am J Med Sci* 267:345-352, 1974.

2. Yee NM, Katz M, Neu HC: Meningitis, pneumonitis and arthritis caused by *Neisseria meningitidis* group Y. *JAMA* 232:1354-1355, 1975.

3. Irwin RS, Woelk WK, Coudin WL: Primary meningococcal pneumonia. *Ann Intern Med* 82:493-498, 1975.

4. Koppes GM, Ellenbogen C, Gebhart RJ: Group Y meningococcal disease in United States Air Force recruits. *Am J Med* 62:661-666, 1977.

5. Breitenbucher RB, Khan MY: Fatal meningococcemia and meningitis due to meningococcus group Y. *Minn Med* 60:240-242, 1977.

6. Griffiss JM, Brandt BL: Disease due to serogroup W135 *Neisseria meningitidis*. *Pediatrics* 64:218-220, 1979.

7. Hersh JH, Gold R, Lepow ML: Meningococcal group Y pneumonia in an adolescent female. *Pediatrics* 64:222-224, 1979.

8. Artenstein MS, Winter PE, Gold R: Immunoprophylaxis of meningococcal infection. *Milit Med* 139:91-95, 1974.

9. Lepow ML, Goldschneider I, Gold R, et al: Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. *Pediatrics* 60:673-680, 1977.

10. Wahdan MH, Rizk F, El-Akkad AM, et al: A controlled field trial of a serogroup A meningococcal polysaccharide vaccine. *Bull WHO* 48:667-673, 1973.

11. Peltola H, Mäkelä PH, Elo O, et al: Vaccination against meningococcal group A disease in Finland 1974-75. *Scand J Infect Dis* 8:169-174, 1976.

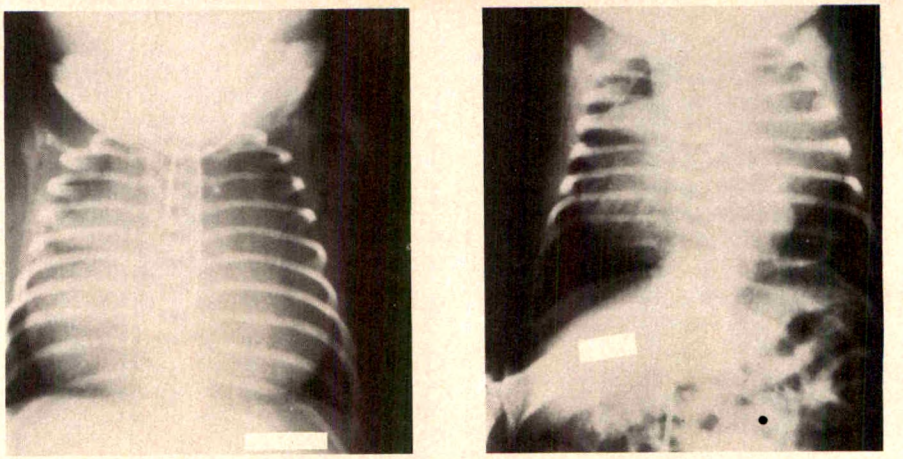
12. Farquhar JD, Hankins WA, Desanctis AN, et al: Clinical and serological evaluation of a meningococcal polysaccharide vaccine groups A, C and Y(39995). *Proc Soc Exp Biol Med* 157:79-82, 1978.

Intrapericardial Teratoma: A New and Treatable Cause of Hydrops Fetalis

Nonimmune hydrops fetalis, characterized by the accumulation of interstitial water (anasarca) in the absence of isoimmunization, has been associated with at least 38 different pathologic entities, accounting in 1970 for approximately 20% of reported hydropic infants.[1-3] Surprisingly, the association of hydrops and congenital heart disease is an uncommon observation,[1] but has been reported sporadically in patients with premature closure of either the patent foramen ovale or ductus arteriosus, Ebstein's anomaly of the tricuspid valve, severe pulmonary insufficiency, both right and left ventricular endocardial fibroelastosis, myocarditis, cerebral, pulmonary, and abdominal arteriovenous fistulae, hypoplastic left heart syndrome, and cardiac arrhythmias.[1] Interestingly, intrapericardial teratomas have been associated with pericardial effusion,[4-8] usually with cardiac tamponade in infants,[4,5,8] but not with hydrops. This report presents the clinical features of a newborn with an intrapericardial teratoma and hydrops fetalis, and discusses the incidence, diagnosis, and management.

Report of a Case.—The patient weighed 3,090 g at birth, the product of a 33-week gestation complicated by polyhydramnios. His mother was 35 years old, gravida 4, para 2, abortus 1, O Rh-negative. At birth he was severely hydropic and had Apgar scores of 2 and 4 at one and five minutes, respectively. His systolic blood pressure was 54 mm Hg; pulse rate, 120 beats per minute; and respirations, 50/min. There was no pulsus paradoxus. Breath sounds were diminished bilaterally. Heart sounds were distant and regular. There were no murmurs. The abdomen was tense and distended. There was severe, generalized edema. By Dubowitz's estimate, fetal age was 34 weeks.

The hematocrit value was 43%; total serum protein level, 2.6 g/dL; BUN level, 13 mg/dL; and serum creatinine concentration, 1.4 mg/dL. The patient's blood type was O Rh-positive; the Coombs' test was negative. Blood, urine, and CSF bacterial cultures were sterile. No virus was grown from either the nasopharynx or stool. Immunoglobin concentrations were normal, and the toxoplasmosis, other (coxsackie, echo, enterovirus), rubella, cytomegalic inclusion, and herpes (TORCH) screen was negative. The chest roentgenogram demonstrated right-sided pleural effusion, with a hazy appearance to the lung fields bilaterally. The heart silhouette was massively enlarged (Figure). An ECG disclosed a right axis, sinus rhythm, and small QRS complexes in all 12 leads. An echocardiogram showed a large amount of fluid in the anterior pericardial space. Initial treatment consisted of fluid restriction and furosemide. Within one week his weight decreased to 2,048 g.



Left, Chest roentgenogram demonstrates massive midline radiopacity. Right, Following intrapericardial instillation of 20 mL of carbon dioxide, note large tumor mass to patient's right, displacing heart and thymus to left.

Two pericardiocenteses yielded 42 mL of fluid; radiologic examination showed no change in the cardiac silhouette. On the 19th day, the patient underwent catheterization of the right side of the heart. The heart and pulmonary arteries were displaced to the left. The foramen ovale could not be crossed. Right atrial pressure was as follows: a wave, 10 mm hg, and v wave, 5 mm Hg (mean, 3 mm Hg); right ventricular pressure, 65/10 mm Hg; and pulmonary artery pressure, 33 mm Hg systolic (mean, 16 mm Hg). There were no left-to-right shunts. Angiograms in the right ventricle, right atrium, and main pulmonary artery demonstrated displacement of the heart to the left, with a concavity to the right atrial silhouette suggestive of an extrinsic mass. After instillation of 20 mL of carbon dioxide into the pericardial space, the chest x-ray film (Figure, right) disclosed a filling defect in the right anterior and superior pericardial space displacing the thymus and heart to the left. The systolic pressure difference between the right ventricle and pulmonary artery was attributed to compression from the intrapericardial mass.

When the patient was 23 days of age, an intrapericardial tumor adherent to the pericardial reflection at the aorta was excised. The 8 × 6 × 5-cm tumor was estimated to be four to five times larger than the heart. At histologic examination, the mass contained immature neurologic tissue (scattered areas of choroid plexus, and eye), colonic epithelium, respiratory tract epithelium, cartilage, and squamous mucosa, diagnostic of a teratoma. No malignant elements were seen. His postoperative course was complicated by aspiration pneumonia that responded to medical management. He has continued to do well at age 20 months.

Comment.—Extensive reviews of hydrops fetalis[1,2] fail to cite intrapericardial teratoma as a cause of hydrops. Similarly, a review of 37 cases of intrapericardial teratoma did not disclose any patients with hydrops.[4] We have identified an additional 14 reported patients with intrapericardial teratoma and pericardial effusion; none has had hydrops fetalis.[5-9,10-13]

Intrapericardial teratomas are rare. Teratomas account for only 10% of mediastinal masses in children.[14] In a recent review of several series of teratomas in children,[14] the anterior mediastinum accounted for only 3% to 5%, and none was reported to be within the pericardium. During an eight-year period, according to D. C. Fyler, MD (written communication, Dec 12, 1978), the New England Regional Infant Cardiac Program identified three patients with an intrapericardial teratoma among 3,376 infants with critical congenital heart disease, a rate of approximately one in 10,000 infants per year with critical heart disease. Nonetheless, at least 50% of the patients with intrapericardial teratomas are initially observed within the first three months of life.[9] Malignant degeneration at the time of original diagnosis is unusual; Reynolds et al[4] described two among their 37 collected cases; we were able to identify only one more[10] in the 14 additional patients. These three patients died with severe local extension of disease.

The pathogenesis of hydrops fetalis is unknown.[1] Although hydrops fetalis is associated with an increased incidence of cardiac malformation, the converse is not true, and no etiologic

relationship between the two has been established.[3] Nonetheless, postulated mechanisms include anemia, congestive heart failure, hypoalbuminemia, decreased colloid oncotic pressure,[1] and, in the patient with congenital structural heart disease, right ventricular obstruction.

Hypoproteinemia was present in our patient (2.6 g/dL); the resultant calculated serum albumin concentration of 1.6 g/dL (60% of total protein) almost certainly resulted in a low oncotic pressure, and no doubt contributed to the anasarca. In addition, the estimated tumor-cardiac ratio (4 to 5:1) very likely produced severe right-sided obstruction at the level of the right atrium, further contributing to the development of hydrops.

The diagnosis of an intrapericardial tumor should be suspected early in the course of an infant with unexplained hydrops and a large heart and should lead to early echocardiogram[6] and cardiac catheterization. Two-dimensional echocardiography, radioangiography,[9] and pneumopericardiocentesis[4,8] may render catheterization unnecessary. As Reynolds and colleagues[4] have emphasized, the treatment is careful diuresis followed promptly by surgical excision. In most patients,[4] the tumor is attached to the heart or great vessels by a fibrous stalk, and bypass of the circulation is unnecessary. Nonetheless, hemorrhage is the major surgical complication. Of the 52 (including ours) patients described in the literature, 35 have been operated on, with 79% survival. There are no reported recurrences of intrapericardial tumor. Thus, despite the low frequency of the lesion, accurate diagnosis is essential as treatment is potentially curative.

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1. Etches PC, Lemons JA: Nonimmune hydrops fetalis: Report of 22 cases including three siblings. *Pediatrics* 1979;64:326-332.

2. Beischer NA, Fortune DW, Macafee J: Non-immunologic hydrops fetalis and congenital abnormalities. *Obstet Gynecol* 1971;38:86-95.

3. Bose C: Hydrops fetalis and in utero intracranial hemorrhage. *J Pediatr* 1978;93:1023-1024.

4. Reynolds JL, Donahue JK, Pearce CW: Intrapericardial teratoma: A cause of acute pericardial effusion in infancy. *Pediatrics* 1969;43:71-78.

5. Lintermans JF, Schoevaertds JC, Fiassel L, et al: Intrapericardial teratoma: A curable cause for cardiac tamponade in infancy. *Clin Pediatr* 1973;12:316-318.

6. Farooki ZA, Hakima ML, Arciniegas E, et al: Echocardiographic features in a case of intrapericardial teratoma. *J Clin Ultrasound* 1978;6:108-110.

7. Lubin BH, Friedman S, Miller WW: Intrapericardial teratoma associated with pericardial effusion. *J Pediatr Surg* 1967;2:336-342.

8. Chalnot P, Pernot C, Frisch R, et al: Intrapericardial teratoma in young infants apropros two cases. *Ann Surg Thorac Cardiovasc* 1968;7:515-521.

9. White JJ, Kabach MN, Haller JA: Diagnosis and excision of intrapericardial teratoma in an infant. *J Thorac Cardiovasc Surg* 1968;55:704-710.

10. Monterio DC: Teratoma of the pericardium in newborn infants: Report of case and literature review. *Rev Hosp Clin Fac Med Sao Paulo* 1968;23:50-56.

11. Zaorski JR, Evangelist FA, Sakibara S, et al: Intrapericardial teratoma: A case report. *Milit Med* 1971;136:582-583.

12. Kulkani MG: Intrapericardial teratoma. *Ann Thorac Surg* 1969;7:30-33.

13. Deenadayala RP, Tuiri D, Dewall RA, et al: Intrapericardial teratoma and bronchogenic cyst: Review of literature and report of successful surgery in infants with intrapericardial teratoma. *J Thorac Cardiovasc Surg* 1974;67:945-952.

14. Bower RJ, Kiesewetter WB: Mediastinal masses in infants and children. *Arch Surg* 1977;112:1003-1009.

Clostridium Infection in Mother and Infant

Clostridium infections in newborns, excluding neonatal tetanus, are rarely reported.[1-7] The case described here is of special interest because both the mother and infant had classic, symptomatic *Clostridium* septicemia and both recovered.

Report of a Case.—A 19-hour-old, 3,080-g, female infant was transferred to North Carolina Memorial Hospital (NCMH) because of jaundice, dark urine, and maternal fever. The infant had been delivered by emergency cesarean section for fetal distress of a 25-year-old, O-positive, primagravida after an uncomplicated term pregnancy. An amniotomy performed 2½ hours prior to delivery had yielded clear fluid. Apgar scores were 6 and 5 at one and five minutes, respectively, after birth. Initial tachypnea and grunting had resolved by 1 hour of age. At 12 hours of age, the infant was jaundiced and passing dark urine. Her total serum bilirubin level was 10 mg/dL (direct bilirubin level, 1.0 mg/dL), and hematocrit value 49%. Cord, throat, stool, blood, and urine cultures had been taken, and 150,000 units of penicillin G potassium and 20 mg of kanamycin sulfate had been given intramuscularly (IM) prior to transfer.

Physical examination and admission to NCMH was normal except for jaundice. There was no fever. The hematocrit value had fallen 12 points over seven hours to 37%. The WBC count was 29,000/cu mm, with a shift to the left. Toxic granulations were seen. The infant's blood type was A positive; the direct Coombs' test was negative, and the indirect Coombs' test was weakly positive for anti-A antibody. The urine was dark brown with marked hemoglobinuria and bilirubinuria, but RBCs were not seen on microscopic examination. The total serum bilirubin level had risen to 15.3 mg/dL. Serum electrolyte values were normal, but the BUN level was 21 mg/dL and the serum creatinine concentration was 1.7 mg/dL. There were scattered patchy infiltrates in the right upper and right lower lobes on chest roentgenogram.

The infant was treated with ampicillin sodium, 150 mg/kg/day, and kanamycin sulfate, 15 mg/kg/day, both given IM. Phototherapy was administered for four days. The maximum total serum bilirubin level was 17.1 mg/dL. On the second day of hospitalization, both the infant's and mother's blood cultures yielded *Clostridium perfringens*. Ampicillin and kanamycin therapy was discontinued, and penicillin G potassium, 200,000 units/kg/day, was administered IM for ten days. The infant remained asymptomatic, with a stable hematocrit value of 34%. Repeated measurements of BUN and serum creatinine levels gave normal values; the follow-up chest roentgenogram at 1 month of age was also normal.

The mother's illness was more severe. Twelve hours postpartum, her temperature was 39.5 °C. She was jaundiced, with a total serum bilirubin level of 6.6 mg/dL. Her WBC count was 15,200/cu mm. Her hemoglobin level had fallen from 12 to 5.7 g/dL, and there was evidence of hemolysis on peripheral blood smear. Marked hemoglobinuria was present. She was transfused with packed RBCs and treated for ten days with aqueous penicillin G and clindamycin phosphate given intravenously. The abdominal wound healed without complications, and she was discharged on the tenth postpartum day. Examination of the placenta showed no evidence of inflammation. Placental cultures were not obtained. Chemical identification and disk sensitivities on the transferred organisms confirmed the identity of the *C perfringens* blood culture isolate from mother and infant.

Comment.—*Clostridium* species can produce major disease in adults, but several reports have noted a poor correlation between the presence of *Clostridium* in soft tissues or in the bloodstream, and clinical sepsis.[8-10] *Clostridium* species are isolated infrequently from neonates, but when

present are found most often in peritoneal, wound, and blood cultures.[11] Recently, *Clostridium* species have been associated with neonatal necrotizing enterocolitis.[12]

The present case of pure *Clostridium* infection in the newborn is the ninth reported, but the first, to our knowledge, confirming simultaneous maternal and infant septicemia. It also appears to be the first neonatal case that demonstrates the classic features of symptomatic adult *Clostridium* septicemia: active hemolysis and resultant hyperbilirubinemia and hemoglobinuria. In general, the presenting signs and symptoms do not discriminate *Clostridium* infection from any other generalized infection in the newborn. Jaundice and/or elevated indirect bilirubin values are mentioned in six of the nine reported cases.[1,2,4-6] Seven (77%) of nine infants had septicemia proved by culture.[1,2,4-7] Two infants had omphalitis only,[1,3] and two had sepsis and omphalitis.[4,7] *Clostridium perfringens* was the species isolated in six (67%) of the nine cases. The mortality was 44% (4/9), and one survivor is severely handicapped.[4] In the two earliest cases,[1] antibiotics were administered together with antiserum. Currently, penicillin in dosages of 50,000 to 200,000 units/kg/day is the drug of choice for *Clostridium* infections, although other antibiotics often are added to cover coinfecting organisms. In cases of tissue infection, it is essential to debride the necrotic material.

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Edward Thorne, MD, referred the infant. John A. Kirkland, MD, provided information on the mother. The Wilson Memorial Hospital Microbiology Laboratory provided the original *Clostridium* isolates.

1. Isenberg AN: *Clostridium welchii* infection. *Arch Surg* 92:727-731, 1966.
2. Freedman S, Hollander M: *Clostridium perfringens* septicemia as a postoperative complication of the newborn infant. *J Pediatr* 71:576-578, 1967.
3. Wilson WR, Martin WJ, Wilkowske CJ, et al: Anaerobic bacteremia. *Mayo Clin Proc* 47:639-646, 1972.
4. Walker SH, Macaraeg EI: Neonatal sepsis due to *Clostridium perfringens*. *Md State Med J* 22:61-62, 1973.
5. Chow AW, Leake RE, Yamauchi T, et al: The significance of anaerobes in neonatal bacteremia: Analysis of 23 cases and review of the literature. *Pediatrics* 54:736-745, 1974.
6. Gorbach SL, Thadepalli H: Isolation of *Clostridium* in human infections: Evaluations of 114 cases. *J Infect Dis* 131(suppl):S81-S85, 1975.
7. Bogdan JC, Rapkin RH: Clostridia infection in the newborn. *Pediatrics* 58:120-122, 1976.
8. Ramsay AM: The significance of *Clostridium welchii* in the cervical swab and blood stream in postpartum and post-abortum sepsis. *J Obstet Gynaecol Br Commonw* 56:247-258, 1949.
9. Rathburn HK: Clostridial bacteremia without hemolysis. *Arch Intern Med* 122:496-501, 1968.
10. Alpern RJ, Powell VR Jr: Nonhistotoxic clostridial bacteremia. *Am J Clin Pathol* 55:717-722, 1971.
11. Dunkel LM, Brotherton TJ, Feigin RD: Anaerobic infections in children: A prospective study. *Pediatrics* 57:311-320, 1976.
12. Kliegman RM, Fanaroff MB, Izant R, et al: Clostridia as pathogens in neonatal necrotizing enterocolitis. *J Pediatr* 95:727-731, 1966.

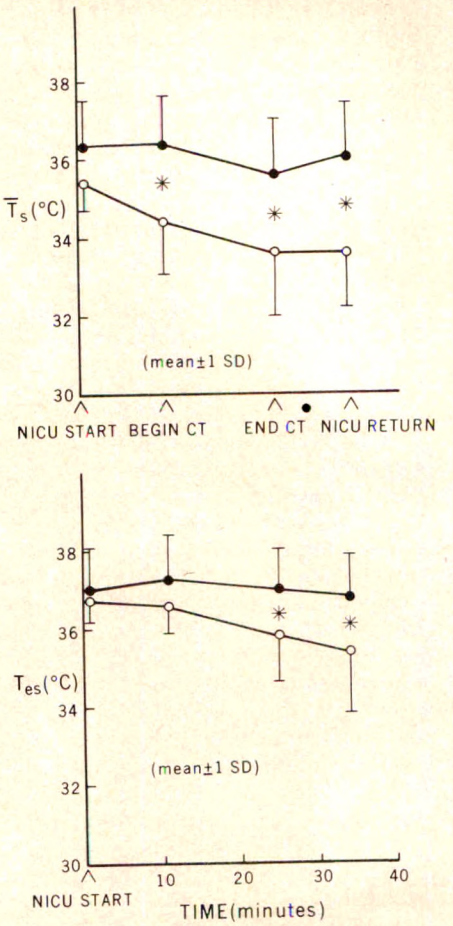
Temperature Control During Computerized Tomography and In-Hospital Transport of Low-Birth-Weight Infants

Computerized tomography (CT) is being used with increasing frequency for the diagnosis of intracranial pathological conditions in low-birth-weight infants. To ensure reliable computer function, ambient temperature in the scanner room is maintained below 23.9 °C. This precludes the use of radiant heaters and subjects small infants to considerable cold stress during the procedure.

We studied temperature control during in-hospital transport and CT scan in 14 infants with a heated mattress as the heat source.

Patients and Methods.—Fourteen infants, with gestational ages between 26 and 34 weeks and birth weights 700 to 2,220 g, were studied two to 63 days after delivery when undergoing CT brain scans. Eight infants received ventilation assistance during the procedure and during transport to and from the Neonatal Intensive Care Unit (NICU). Skin temperatures were measured at six sites, and mean skin temperature was calculated with weighted factors from measurements of surface area.[1] Core temperature was measured in the esophagus.

Six infants were studied using the heated mattress as the sole source of heat (group 1). Eight infants were warmed by the mattress in addition to being wrapped in bubble plastic packaging material (group 2). Mean weight (± SD) at the time of the study was 1,352 ± 620 g in group 1 and 1,098 ± 587 g in group 2. All infants wore wool boots and caps. The infants were transported in their own single-walled incubator, with full monitoring throughout the procedure.



Mean skin temperature ($\bar{T}_s$) and esophageal temperature (T_{es}) of infants during in-hospital transport and computerized tomographic (CT) scan. NICU indicates neonatal intensive care unit. Closed circle indicates heated mattress plus bubble plastic bag (n = 8); open circle, heated mattress (n = 6). Asterisk indicates $P<.05$.

Results.—The Figure shows the mean skin and esophageal temperatures recorded before, during, and after CT scan. A combination of the heated mattress and a simple insulating bag (group 2) maintained body temperature throughout (although these infants were considerably lighter), whereas a significant fall in body temperature occurred by the end of the procedure in the infants in group 1. Hyperthermia occurred transiently in two infants in group 2 before they left the NICU (core temperature, 38.1 °C and 38.4 °C, respectively).

Comment.—Both the heated mattress and the transparent baby bag have been used previously with success in situations where the infant is exposed to thermal stress.[2,3] After a two-hour recycling process when ener-

gy is stored in the liquid phase, the heating system is activated by injection of a small amount of catalyst into the liquid contents of the mattress. A reaction characterized by an exothermic latent heat of recrystallization occurs within a few seconds and will maintain the temperature of the mattress at 40 °C for two to four hours, depending on the ambient temperature. Thirteen of the neonates who required CT brain scans had sustained an intraventricular hemorrhage and were critically ill, so their mechanisms for thermal homeostasis were inadequate even with minor cold stress. This sort of stress is unavoidable during the performance of a CT scan, and the combination of the heated mattress and bubble plastic bag was effective in preventing a fall in body temperature, both during the scan as well as during the transport of the infant. The mattress by itself did not prevent hypothermia (Figure). The availability of a portable heat source together with a simple insulating blanket made it possible to transport these infants without removing them from their own incubators to a transport incubator, thus simplifying the whole process considerably. The potential for hyperthermia to develop when this technique is used necessitates close monitoring of the infant's temperature.

This is a simple, efficient, inexpensive, and convenient method for maintaining body temperature in low-birth-weight infants during transport and during the performance of procedures in the hospital.

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1. Silverman WA, Agate FJ Jr: Variation in cold resistance among small newborn infants. *Biol Neonate* 1964;6:113-127.
2. Besch NJ, Perlstein PH, Edwards NK, et al: The transparent baby bag: A shield against heat loss. *N Engl J Med* 1971;284:121-124.
3. Nielsen HC, Jung AL, Atherton SO: Evaluation of the Porta-Warm mattress as a source of heat for neonatal transport. *Pediatrics* 1976;58:500-504.

60 YEARS AGO IN THE AJDC

Some Phases of the Pathology of Nutrition in Infancy

In this paper read before the Harvey Society is an extensive review of the current understanding of acute diarrhea (toxicosis or cholera infantum) and of more chronic marasmus (infantile atrophy, athrepsia). Both conditions are common and cause large numbers of infant deaths. Since there is little anatomic pathology observed in these disorders, a derangement in the chemical and physiologic process must be suspected.

In the acute form, rapid loss of weight occurs with sharpening of the features, sunken eyes, loose skin, and dry lips and mouth. Respirations are deep with "air hunger," thought due variously to circulating abnormal acids, a loss of base, or a loss of renal phosphate excretion. The gray pallor and prostration with a weak thready pulse are caused by diminished blood volume due to drying of the blood by excessive water loss. There is some similarity to surgical shock except that plasma proteins are found to be high in diarrhea. Reducing substances, detected in the urine, have been shown to be glucose, galactose, or lactose. The latter, not altered in the body outside of the intestinal tract, is then excreted in the urine. The fever which so commonly occurs has been thought by Finkelstein due to the effect of a pyrogen, but Woodyatt and his associates felt it was due to a decrease in the amount of water available for evaporation since the healthy infant has been shown to lose 2½ times as much as an adult through this route.

Various ideas of causation have been proposed: excess of fat or carbohydrate, parenteral origin, infectious agents, and injudicious use of cathartics. Heubner pointed out its similarity to Asiatic cholera, known to be of an infectious nature.

Therapeutically it is known that if the infant is given food, especially an excess of fat or carbohydrate, the diarrhea becomes worse and that soluble metabolites in the blood increase the osmotic pressure and decrease available water reserve. Thus it is necessary to provide sufficient fluids. It is impossible to accomplish this by oral administration. Ringer's solution or physiologic sodium chloride may be given subcutaneously and a small amount intravenously. However, the most efficient means of introducing water to these infants is by way of the peritoneal cavity as employed extensively by Howland. Alkali administration is unnecessary to correct the acidosis unless of a severe degree, as this disappears when a sufficient amount of fluid is given.

The chronic condition of malnutrition, marasmus, develops insidiously and may accompany various disorders, but the ultimate fate is similar. The infant wastes to a skin-covered skeleton with cold extremities, a slow pulse, and low body temperature. The urine is usually normal but for a higher ammonia coefficient. A negative nitrogen balance exists. The blood volume may be normal, acidosis does not occur, and the circulation is undisturbed. Prolonged underfeeding is the most common cause, and once the condition is fully developed the tolerance for food may be so low that it is impossible to give a sufficient amount to cover even the basal energy requirements. Breast milk appears to be better tolerated and it is thought that the protein of cow's milk may be harmful. These infants need calories, protein, and mineral salts and the necessary accessory substances known as vitamins. Fat is not well tolerated and large amounts of carbohydrate cannot be used without producing irritation of the intestinal tract. Though the therapeutic indications are clear, they are too often difficult or impossible to fulfill.—W. McKim Marriott, Department of Pediatrics, Washington University, and St Louis Children's Hospital, St Louis (20:461-485, December 1920).

Letters to the Editor

Correspondence pertaining to material published in the JOURNAL will be published, if found suitable, as space permits. Submit double-spaced copy clearly marked "For publication" and signed by all authors; references should conform to JOURNAL format; maximum length: 500 words. Copyright assignment signed by all authors is required. The Editor reserves the right to edit such letters, which should be received within six weeks of publication of the JOURNAL article in question.

PNU Intoxication

Sir.—Drs Johnson, Kubic, and Levitt presented an informative discussion of the toxic condition caused by accidental ingestion of *N*-3-pyridylmethyl *N'-p*-nitrophenyl urea (PNU, Vacor rat killer) (JOURNAL 134:161-164, 1980). Their patient fortunately recovered, as has been the case with several children with PNU intoxication known to me. Because further studies[1-5] of PNU have amplified the clinical and toxicological information presented in this article, I would like to add some comments to their report.

Among adult patients ingesting various doses of PNU, ketosis-prone hyperglycemia, orthostatic hypotension, gastrointestinal hypomotility, and peripheral neuropathy were prominent features in most cases; in some, signs of encephalopathy also developed.[1] Orthostatic hypotension has been the most important lasting disability, whereas some of the other symptoms tended to improve. The neurological and diabetic complications may develop within hours or days after PNU ingestion and may progress in spite of administration of the proposed antidote, niacinamide.

The current understanding of PNU toxicity is more advanced than the authors intimated. Studies of PNU by the manufacturer have investigated the organ disposition,[6] metabolic and pharmacological interactions,[7] and biotransformation (F. W. Deckert, Rohm and Haas Co, personal communication). Of note is the apparent lack of any PNU toxic reaction in primates or several other animal species. It may be misleading to extrapolate from the animal toxic reactions of compounds with some similarity to PNU the situation of human toxic conditions; streptozocin, for example, proves to be a poor rodenticide, whereas PNU does not readily produce diabetes in rats. 6-Aminonicotinamide,[8] a niacinamide antagonist that produces a toxic condition in rodents similar to that produced by PNU, has not produced in experimental human use the spectrum of toxic reactions associated with PNU.[9] Hence, the pharmacological considerations of PNU toxicity are, at this time, largely speculative.

The optimal therapy for PNU poisoning includes the use of parenteral niacinamide, as suggested by animal intoxication data. If niacinamide is not on hand, however, immediate therapy should be undertaken with whatever form of the vitamin is available (such as multivitamin preparations) since the body is capable of interconversion of the various forms of niacin. Attempts at inducing emesis and catharsis, as advocated in the report by Johnson et al, may be ineffective in the face of the ileus and esophageal hypomotility produced by PNU. I would recommmend extensive effort at gastric and enteral drainage to remove any residual toxin. Doses of niacinamide larger and more frequent than what were advised are probably not contraindicated. An additional therapeutic strategy might be beneficial, if I may indulge in some speculative toxicology: 6-aminonicotinamide toxic reaction was reversed in dogs with the use of corticosteroids,[10] and this untested therapy might conceivably be effective in human PNU intoxication. A treatment for the orthostatic hypotension has been previously discussed.[1]

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1. LeWitt PA: The neurotoxicity of the rat poison Vacor. *N Engl J Med* 302:73-77, 1980.

2. Glascow JL, Bonar JR, Tucker TS: Diabetes induced by Vacor rat killer. *Diabetes* 25:365, 1976.

3. Lee TH, Kang JC, Han MD, et al: A clinical analysis of rodenticide RH-787 intoxication in Korea. *Korean Diabetic J* 4:43-51, 1977.

4. Lee TH, Kim YS, Chung MY, et al: Clinical prospective study of rodenticide RH-787 intoxication in humans. *Korean J Intern Med* 20:530-537, 1977.

5. Pont A, Rubino JM, Bishop D, et al: Diabetes mellitus and neuropathy following Vacor ingestion in man. *Arch Intern Med* 139:185-187, 1979.

6. Deckert FW, Hagerman LM, Lisk DC, et al: The disposition of ^{14}C-RH-787 (Vacor rodenticide) in rodents and dogs. *Toxicol Appl Pharmacol* 45:313, 1978.

7. Deckert FW, Godfrey WJ, Lisk DC, et al: Metabolic interactions with RH-787 (Vacor rodenticide). *Fed Proc* 37:424, 1978.

8. Herken H, Lange K, Kolbe H, et al: Antimetabolic action on the pentose phosphate pathway in the central nervous system induced by 6-aminonicotinamide, in Ganazzani E, Herken H (eds): *Central Nervous System: Studies on Metabolic Regulation and Function*. Berlin, Springer Verlag, 1974, pp 189-203.

9. Herter FP, Weissman SG, Thompson HG, et al: Clinical experience with 6-aminonicotinamide. *Cancer Res* 21:31-37, 1961.

10. Greengard P, Sigg EB, Fratta I, et al: Prevention and remission by adrenocortical steroids of nicotinamide deficiency disorders and of 6-aminonicotinamide toxicity in rats and dogs. *J Pharmacol Exp Ther* 154:624-631, 1966.

Treatment and Prophylaxis Failure of Erythromycin in Pertussis

Sir.—The report by Halsey and associates (JOURNAL 134:521-522, 1980) deserves critical review. They observed an infant with clinical pertussis, the culture being positive; after only seven days of erythromycin therapy, the infant was found on the eighth day to have a positive culture for *Bordetella pertussis*. The fluorescent antibody (FA) test on the same sample was negative. This does not necessarily indicate an erythromycin treatment failure.

Short courses of erythromycin are often followed by bacteriologic relapse. We observed such a relapse in the first of ten patients treated with erythromycin in our study of pertussis.[1] This patient had negative culture and FA test after 48 hours of treatment. She was treated for ten days, and one day after stopping erythromycin therapy she again had positive culture and FA test; this persisted for four days. We did not (and have not since) observed a bacteriologic relapse in patients treated for 14 days. In the patient described by Halsey et al, the negative FA test on the same specimen that had positive culture suggests a substantial suppressive effect of erythromycin on the organism.

The authors also observed a second infant in whom clinical pertussis with positive culture developed after three days of erythromycin therapy. However, erythromycin was not begun until at least five days after exposure. They interpreted this as a failure of prophylaxis, but this is not a fair test. It more likely represents failure to abort an incubating infection. The mild and short subsequent course of illness suggests that the disease may have been favorably modified. Apparently, pertussis organisms were not recovered from the second patient after the original isolation.

It is unfortunate that the organisms isolated from both patients were lost before antimicrobial sensitivity studies could be performed. To our knowledge, erythromycin-resistant *B pertussis* organisms have not been reported.

We concur that studies evaluating erythromycin prophylaxis against pertussis in susceptible contacts are needed. Passive protection cannot be achieved with pertussis hyperimmune globulin, and no antimicrobial agent has shown as much promise as has erythromycin in preventing or modifying the disease. Until such studies are available, there appears to be enough evidence, adequately referenced in the report of Halsey et al, to continue use of erythromycin in the treatment of pertussis. It will render the cultures of patients negative, and they will be presumably noncontagious. In susceptible patients exposed to persons with pertussis of positive culture, the drug may prevent or clinically modify the disease as well as render the patients' cultures negative and thus help curb spread of the disease in epidemic situations.

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Gastroschisis

Sir.—Carlos F. Salinas and associates have reported the occurrence of gastroschisis in siblings (JOURNAL 133:514-517). My experience shows that gastroschisis and omphalocele can occur in siblings and suggests that the former condition also represents anomaly of the umbilical ring.

Report of Cases.—CASE 1.—This male infant was born after a 34-week gestation to a 23-year-old primigravida, para 1 woman and her 18-year-old husband. The infant weighed 2,140 g and had eviscerated, thickened intestines with malrotation, protruding through a 5-cm cleft to the right side of an intact umbilicus. Surgical closure of the defect was performed. He is now 5 years old. We found no history of abdominal-wall defect in the family.

CASE 2.—The boy's sister was a full-term stillborn infant with a huge umbilical omphalocele and no additional anomalies.

Comment.—To our knowledge, familiar occurrence of omphalocele and gastroschisis has not been hitherto reported.

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Heart Failure and Cystic Fibrosis

Sir.—Stern et al, in their article "Heart Failure in Cystic Fibrosis" (JOURNAL 134:267-272, 1980), reconfirmed both the dismal outlook for cystic fibrosis (CF) patients in whom overt right-sided heart failure develops and the relative lack of efficacy of digitalis in treating overt failure.[1] However, two questions arise. Fishman[2] has described an escalating continuum of pulmonary hypertension, cor pulmonale (secondary enlargement of the right ventricle), and overt right-sided heart failure. The patients described by Stern et al fall into the last category. Do the authors have data on the efficacy of treatment of patients with pulmonary hypertension or with cor pulmonale without overt right-sided heart failure?

The second question concerns the mixed venous P_{O_2} ($P\bar{v}O_2$) of these patients. Mithoefer et al[3] studied the relationship of arterial blood gases (ABG) to $P\bar{v}O_2$ in 55 adult patients with chronic obstructive lung disease. However, their diagnoses were not specified. They found that the $P\bar{v}O_2$ was fairly predictable on the basis of the ABG. If the $PaCO_2$ was normal (ie, < 44 torr) and the PaO_2 was 63 torr or more, $P\bar{v}O_2$ was normal (≥ 34 torr). In the hypercapnic group ($PaCO_2 > 46$ torr), a lower PaO_2 (50 torr) was the cutoff point for a normal $P\bar{v}O_2$. Estimation of the $P\bar{v}O_2$ is important because it is believed to be a reliable index of tissue P_{O_2}[4] and because in patients with large anatomic shunts, a fall in $P\bar{v}O_2$, per se, may worsen arterial hypoxemia. This is of some interest since the cachexia seen in adolescents and young adults with CF is *not* explained by steatorrhea and azotorrhea but is more closely correlated with the degree of pulmonary disease.[5] If the $P\bar{v}O_2$ reflects tissue P_{O_2}, then the $P\bar{v}O_2$ may be an important factor for prognosis in these patients.

The ABG data of Stern et al would place all of their patients into either of the two low-$P\bar{v}O_2$ categories of Mithoefer et al. Do the authors have data that would confirm the relationship of $P\bar{v}O_2$ to the ABG in patients with CF or that would correlate $P\bar{v}O_2$ with survival?

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1. Green LH, Smith TW: The use of digitalis in patients with pulmonary disease. *Ann Intern Med* 87:459-465, 1977.
2. Fishman AP: Chronic cor pulmonale. *Am Rev Respir Dis* 114:775-794, 1976.
3. Mithoefer JC, Ramirez C, Cook W: The effect of mixed venous oxygenation on arterial blood in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 117:259-264, 1978.
4. Tenney SM: A theoretical analysis of the relationship between venous blood and mean tissue oxygen pressures. *Respir Physiol* 20:283-290, 1974.
5. Lapey A, Kattwinkel J, diSant'Agnese PA, et al: Steatorrhea and azotorrhea and their relation to growth and nutrition in adolescents and young adults with cystic fibrosis. *J Pediatr* 84:328-334, 1974.

In Reply.—We have no catheterization data on pulmonary hypertension in patients with CF prior to the onset of overt right-sided heart failure and thus are unable to evaluate any treatment measures at this stage of the disease. Long-term controlled studies of many moderately involved patients with CF would be necessary and, to our knowledge, this type of information will not be available for many years.

With regard to the questions concerning $P\bar{v}O_2$, all of our patients had abnormal values (<34 mm Hg) and all

also had arterial Po_2 below 50 mm Hg. In this group, therefore, we are unable to comment on the relationship between a variety of arterial Po_2 values and the $P\bar{v}o_2$. A preliminary examination of $P\bar{v}o_2$ data in our patients (analyzable data are available on 25 of the 31 patients catheterized) does not suggest a clear indication of a relationship with survival. The mean Po_2 for the entire group was 23.7 mm Hg (range, 12 to 33 mm Hg), and the mean Po_2 for the five patients with the longest survival (on whom data are available) was 23.6 mm Hg.

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Screening Newborns for Sickle Cell Anemia

Sir.—Rubin and Rowley's article in the JOURNAL (1979;133:1248-1250) and Miller's editorial in the JOURNAL (1979;133:1235-1236) on newborn screening for sickle cell anemia both suggest that in addition to the problems that can arise through difficulty in making a diagnosis of sickle cell disease during the postnatal period, there is the following problem: confusion within the medical profession both as to methods of diagnosis and definition and to the clinical picture of the varying clinical syndromes. β Thalassemia occurs in the following two forms in the black population: β^+, in which varying amounts of hemoglobin (Hb) A are produced, and β°, in which no Hb A is produced. *Both* are characterized by a low mean corpuscular volume (MCV), an elevated Hb A_2 level, and unbalanced α to β synthesis.

As Drs Rubin and Rowley indicate, the clinical picture may vary from a totally benign course to one indistinguishable from Hb SS disease. Current knowledge would suggest that the β^+ form is the most benign. Clinical studies are currently under way that should clarify these syndromes further. But even on the basis of current knowledge, it is probably essential to be certain to designate whether the β thalassemia under discussion is of the A- (β^+) or non-A (β°)-producing type. This the authors fail to do in their rather confusing discussion of the clinical syndrome or syndromes.

Hemoglobin S/hereditary persistence of fetal hemoglobin (HPFH) is a rare syndrome that (to my knowledge) has to date only been described as a totally benign laboratory finding with no anemia and no changes in the MCV. As more clinical cases are described, whether the clinical picture will continue to be consistently benign remains to be seen. It should also be noted that there have been recent reports of HPFH trait occurring in blacks where the distribution of Hb F is not homogeneous.

The complexities of accurate hemoglobin genotype diagnosis are further confused by several statements in Dr Miller's editorial. It is not true that "citrate agar gel electrophoresis at a pH of 6.2 will permit differentiation of sickle cell anemia from Hb S/HPFH and Hb S/β-thalassemia." The presence of an A_2 band will suggest that the patient has a β thalassemia gene, but no further information is gained about the nature of the F band. Such information can only be gained by procedures such as the Kleihauer-Betke stain, and perhaps more importantly from family studies. This is particularly true in the postnatal period, when Hb F levels are uniformly high and accurate diagnosis is needed.

Family studies are key. It is inconceivable that any properly trained, responsible physician would attempt to counsel a family about any genetic disorder without first attempting to screen the parents. (At different times in the clinical course of the infant as described, the mother could have had any one of the following genotypes: AS, SS, Aβ^+ thalassemia, Hb A/HPFH, Sβ^+ thalassemia, Hb S/HPFH, β^+ thalassemia/HPFH, and possibly others.) How else can the family be given accurate information?

Dr Miller has missed the point. The inaccuracy of a presumptive diagnosis by the New York State Screening Laboratory should not be allowed to obscure the inadequacies of resources for follow-up through parental testing; neither does the general medical community appear to be well enough educated to answer this role. It is hoped that through the recent acquisition of additional federal funding for education, screening, and counseling this distressing situation will change.

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Sir.—We read with interest the report by Drs Rubin and Rowley and the editorial by Dr Miller in the JOURNAL (1979;133:1248-1250 and 1235-1236). There is an apparent misunderstanding about the procedures used to identify newborns with sickle cell anemia and its variants in the New York State Newborn Screening Laboratories. In the presence of Hb S or Hb C on the filter paper blood specimen tested by both cellulose acetate and citrate agar electrophoresis, a repeat blood sample is requested. The repeat specimen (microcapillary) is again tested by both types of electrophoresis before the result is mailed to the physician in charge of the infant in the hospital of birth.

It is unfortunate that citrate agar electrophoresis cannot distinguish between Hb SS, S/β° thalassemia, and Hb S/HPFH, as has been suggested by Dr Miller in his editorial. The Newborn Screening Laboratories are equipped to make diagnoses of Hb SC, Hb SD, Hb SS, Hb AS, Hb AC, and other rare hemoglobinopathies.

According to the guidelines set by the State Commissioner of Health, the results of sickle cell testing are mailed by the Newborn Screening Laboratory to the hospital where the infant was born. The correspondence should clearly state that results are obtained through *screening* tests and place the responsibility for the definitive diagnosis with the physician who will be following up the child.

Since the diagnosis of Hb S/HPFH cannot be made from the infant's blood at birth, the diagnosis is made in later infancy on clinical grounds (ie, the benign course of the condition) and by laboratory data through absence of evidence of hemolysis, the presence of Hb S but no Hb A on electrophoresis, a high Hb F level (15% to 35%), and the demonstration of a uniform distribution of Hb F in a blood smear stained by Kleihauer-Betke stain. The diagnosis can be made at birth if both parents are available for testing and if the test

results show one to have HPFH and the other to have Hb AS. In the family of reference, neither confirmatory testing nor family studies were obtained appropriately on first hospitalization.

The frequency of HbS/HPFH is expected to be very low[1] despite the figures found in the series reported by Kramer et al.[2] However, there will be a rare "benign positive" case referred to as SS, resulting in unnecessary anxiety to the parents. The physician following up the infant must make the definitive diagnosis accurately and expeditiously and reassure the parents if the original diagnosis was erroneous.

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1. Motulsky AW: Frequency of sickling disorders in United States blacks. *N Engl J Med* 1973;288:31.

2. Kramer MS, Rooks Y, Johnston D: Accuracy of cord blood screening for sickle hemoglobinopathies: Three- to five-year follow-up. *JAMA* 1979; 241:485-486.

Sir.—The report of Rubin and Rowley and the accompanying editorial concerning Hb S and HPFH in a newborn was of interest to us (JOURNAL 1979;133:1248-1250 and 1235-1236). We have recently found a similar patient in our newborn screening program. However, we take exception to the statement that acid agar electrophoresis permits differentiation of sickle cell disease from Hb S/HPFH and Hb S/β thalassemia. The agar adds nothing to the differential diagnosis. As indicated by Rubin and Rowley, differentiation requires family study and/or other methods for establishment of the genetic basis for the Hb FS phenotype. We are also confused by the final comment in the editorial about the low incidence of sickle cell anemia in patients without Hb A.

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Sir.—I want to make a brief comment about the statement that citrate agar electrophoresis at a pH of 6.2 will permit differentiation of sickle cell anemia from Hb S/HPFH and Hb S/β thalassemia that appeared in the editorial by Miller in the December 1979 issue of the JOURNAL (1979;133:1235-1236).

Citrate agar electrophoresis at an acid pH may permit the clear recognition of small amounts of Hb A and Hb S in cord blood and aid in the diagnosis of sickle-β^+ thalassemia. However, citrate agar electrophoresis (in cases with an absence of Hb A) will not permit the differentiation of homozygous sickle hemoglobinopathy from sickle-β° thalassemia, sickle-β°/HPFH, and sickle-$\delta\beta$ thalassemia. The differentiation of homozygous sickle hemoglobinopathy from these syndromes may require other studies, including the quantitation of Hb F and Hb A_2, Kleihauer-Betke staining for the study of distribution of Hb F, hematological evaluation (complete blood cell count, smear evaluation, and irreversible sickle cells), in vitro globin-chain synthetic ratio determination, and family studies. While the value of these tests in sorting out some of the sickle syndromes involving the β globin locus in the adult is reasonably understood, they may be of little value in the newborn. As pointed out in the editorial, family studies, when available, are clearly valuable in this setting.

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In Reply.—Dr Smith would have preferred that our differential diagnosis of the proposita deal more extensively with β^+ vs β° thalassemia and the difference in their clinical presentation. We point out that the differential diagnostic process for newborns differs from that appropriate for the symptomatic child in that there is no clinical history. The differential diagnosis is that of a hemoglobin composition, not that of a clinical course. The hemoglobin composition of the proposita described (principally Hb S without Hb A) automatically excludes sickle-β^+ thalassemia, and therefore it was not discussed. As explained in the third paragraph of the "Comment" section, it is sickle-β° thalassemia that must be distinguished from sickle cell anemia because in both there is no synthesis of Hb A.

Drs Grover and Wethers claim that, in the family described, "neither confirmatory testing nor family studies were obtained appropriately." Regarding confirmatory testing, as the article states,

> The presence of an unusually high level of fetal hemoglobin past the neonatal period, the absence of sickle hemoglobin in one parent, the even distribution of Hb F among the RBCs, and the balanced synthesis of α and non-α globin chains, all of which were demonstrated in the twins reported here, confirm the diagnosis.

Regarding family studies, the data supporting the diagnosis of HPFH trait in the mother was presented and was essential to establish the diagnosis of sickle cell trait/HPFH trait in the proposita. Indeed, the family illustrates the fact that in cases where one parent is not available, as we described to be the case here, finding no Hb S in one parent suffices to rule out homozygous Hb S disease in the child.

Dr Smith states, "It is inconceivable that any properly trained, responsible physician would attempt to counsel a family about any genetic disorder without first attempting to screen the parents." We agree that parental testing is an essential part of the diagnosis of sickle cell anemia. However, physicians in our area who receive reports of sickle cell disease in a child under their care are generally not testing parents. We have learned this from our follow-up study of the first 25 cases of sickling hemoglobinopathies diagnosed by state-mandated newborn screening in western New York State.

There are two ways to remedy the current lack of parental testing. The one advocated by Drs Grover and Wethers is for the state's report to the physician to clearly indicate that the result is presumptive and that definitive diagnosis is the responsibility of the physician. The second, which is proposed by us in the article's penultimate paragraph, is for the state, when requesting a second blood sample from the child, to require samples from the parents as well. We do not oppose educating physicians; in fact, we devote much of our time to this activity. However, we believe that the

state, which is providing a medical service that the family has not requested, has the responsibility to protect the family against the false diagnosis of a disease that is often fatal in early childhood. The unfortunate consequences of the latter are illustrated by the family described. Testing of the parents by the state at the time of confirmatory testing of the infant may help avoid the parental anxiety that Drs Grover and Wethers aptly term "unnecessary."

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Dr Rubin is now with the University of California at San Francisco.

1. Steinberg WN, Humbert J, Rowley PT: Impact of diagnosis of sickle cell disease at birth on physicians and on parents, abstracted. *Am J Hum Genet* 1979;31:126A.

In Reply.—Dr Smith, Drs Grover and Wethers, Dr Detter and colleagues, and Dr Rao have correctly emphasized that citrate agar electrophoresis at an acid pH will not differentiate homozygous sickle cell anemia from sickle cell variants associated with thalassemia syndromes and HPFH. It will facilitate the detection of small amounts of Hb A and clearly separate Hb F from Hb S.[1] On that point I stand corrected.

As stated in the editorial (JOURNAL 1979;133:1235-1236) and as presented in the article by Rubin and Rowley (JOURNAL 1979;133:1248-1250), additional laboratory studies on the newborn and on family members are absolutely mandatory before a definitive diagnosis of homozygous sickle cell anemia can be made. My concerns are with the responsibilities of the state screening programs. What will the pediatrician do with information provided by repeated testing that confirms the original result of "consistent with sickle cell anemia"? This is the problem. To avoid misdiagnosis and the attendant emotional trauma to the family, responsible state screening programs, in confirming the absence of Hb A, should recognize the alternative diagnoses (sickle cell trait/HPFH, sickle cell trait/β^+ thalassemia, sickle cell trait/β° thalassemia, and sickle cell/Hb D disease) and clearly instruct the pediatrician that additional studies are mandatory before a definitive diagnosis of sickle cell disease can or should be made. To avoid recurrences, the state laboratory should add an educational function to its existing screening program. With clearer guidelines and suggestions from the screening program (eg, hematology consultation, with additional laboratory and family studies) the practitioner can proceed logically before acting on inaccurate laboratory reports and treating when there is no disease.

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1. Schneider RG: Developments in laboratory diagnoses, in Abramson H, Bertles JF, Wethers DL (eds): *Sickle Cell Disease: Diagnosis, Management, Education and Research.* St Louis, CV Mosby Co, 1973, pp 230-243.

Prune-Belly Syndrome

Sir.—The article by Siebert entitled "Small-Intestine Length in Infants and Children" (JOURNAL 1980;134:593-595) reports one instance of an intra-abdominal lesion in which the small-intestinal length was greater than 2 SDs from the expected mean length. This was in an infant with the prune-belly syndrome in whom the expected small-intestinal length was 164 ± 54 cm (1 SD) and the observed length was 294 cm, greater than 2.4 SDs from the expected mean. One possible explanation for this observation is that linear growth of the small intestine is, in part, determined by the tension on it and the space available for it. When there is lax or absent abdominal wall musculature, as in the prune-belly syndrome, there will be greater intra-abdominal volume and thus additional growth of the small intestine can be accommodated. A similar explanation has been suggested as the basis of linear growth of another tube-like structure, the umbilical cord.[1]

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1. Miller ME, Higginbottom MC, Smith DW: Intrauterine constraint as a cause of short umbilical cord, abstracted. *Pediatr Res* 1980;14:586.

In Reply.—I thank Dr Miller for his interesting comments on elongation of the small intestine in the prune-belly, or abdominal muscular deficiency, syndrome. There are additional data with regard to small-intestinal length with which one may study the possible effect of constraint on developing tissues. In six infants with congenital diaphragmatic hernia, the mean small-intestinal length was 39 cm shorter than normal, although within 1 SD. In two cases of omphalocele, the mean small-intestinal length was decreased by 76 cm, beyond 1 SD. Likely reasons for this tendency toward abnormal shortening seem to conflict, however. If the pleural space in diaphragmatic hernia or the omphalocele sac serve as extensions of the abdominal cavity, then there seems to be increased space in which the small intestine can develop. In this instance, one might expect elongation of the small intestine to occur, vis-à-vis the Miller hypothesis. Conversely, in the two malformations, varying lengths of intestine are sometimes encountered within the pleural cavity or omphalocele sac, rather than in the abdominal cavity per se. These secondary cavities are considerably smaller than the usual peritoneal space and possibly produce a degree of constraint on the growing intestine. The constriction, if it occurs, must be mild, for changes due to severe hypoxia, torsion, or incarceration are generally not seen in the intestinal tract and symptoms are primarily respiratory ones in infancy.[1] Shortening is probably not due to deficient mesenteric attachments, for the mean small-intestinal length in eight cases of isolated malrotation was mildly elongated, but well within 1 SD. Whether two populations exist, ie, those intestinal tracts that develop within extended abdominal cavities and those constrained by ectopic ones, is not known presently.

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1. Warkany J: *Congenital Malformations.* Chicago, Year Book Medical Publishers Inc, 1971, pp 753-755.

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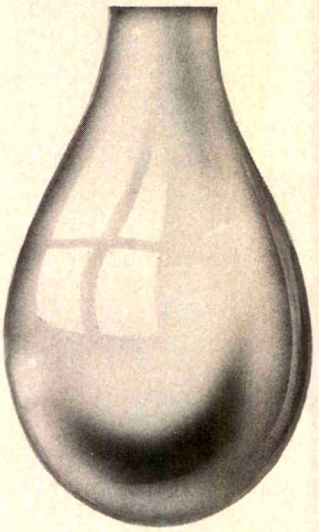

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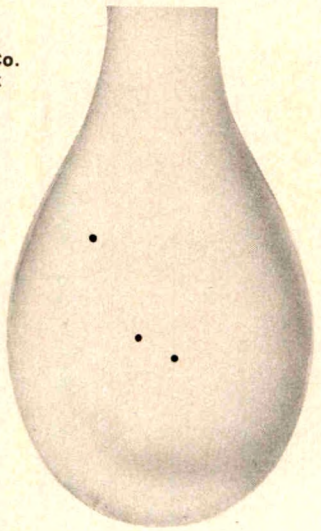

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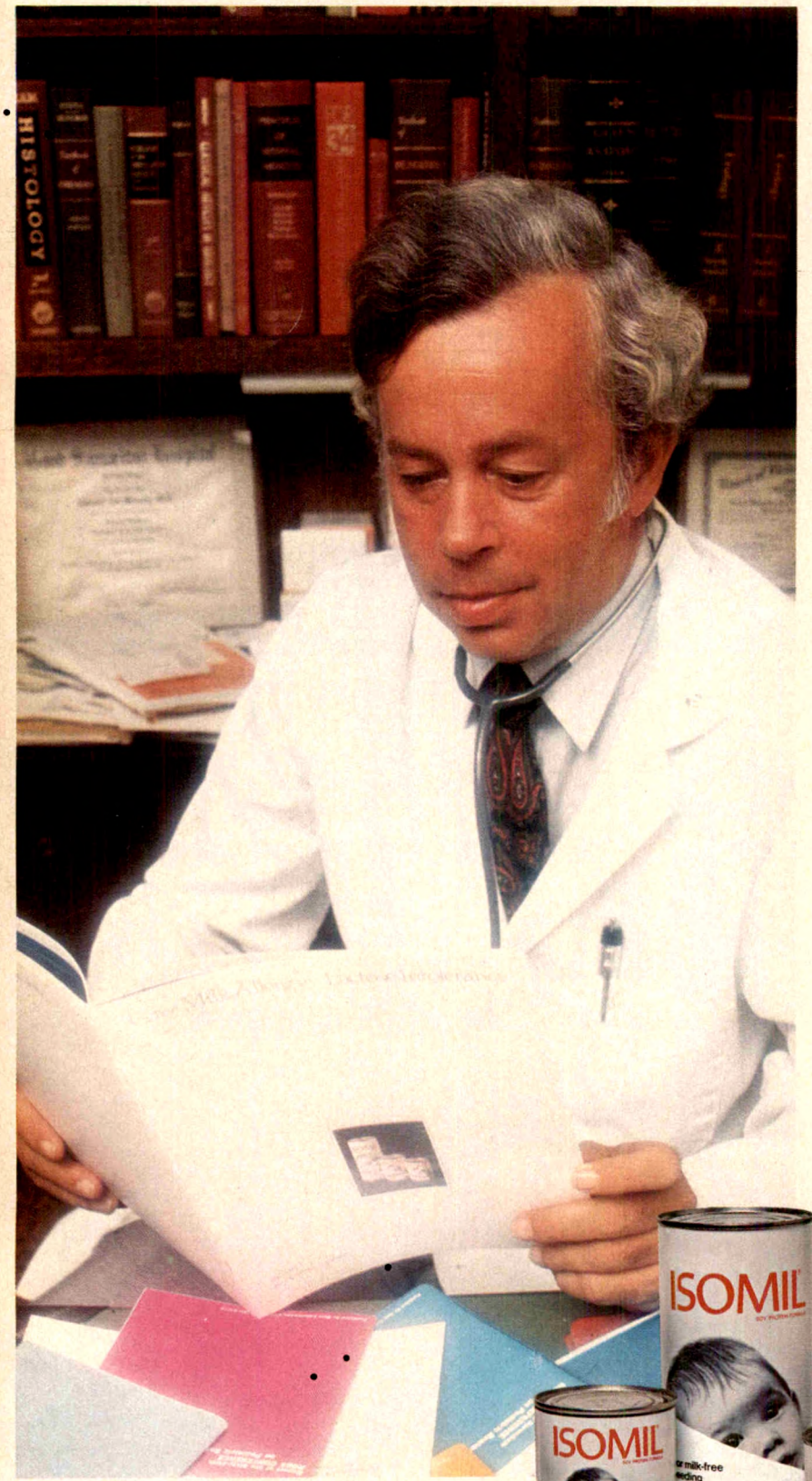

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References:

1. Dean ME: A study of normal infants fed a soya protein isolate formula. *Med J Aust* 1:1289, 1973.
2. Jung AL, Carr SL: A soy protein formula and a milk-based formula. *Clin Pediatr* 16:982, 1977.
3. Leake RD, Schroeder KC, Benton DA, et al: Soy-based formula in the treatment of infantile diarrhea. *Am J Dis Child* 127:374, 1974.
4. Gabr M, Maraghi S, Morsi S: Management of lactose intolerance secondary to acute diarrhea with a soy-based, lactose-free formula. *Clin Therapeutics* 2:271, 1979.

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **INDICATIONS**

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Lacking in substantial evidence of effectiveness as a fixed combination: For relief from coughing, upper respiratory congestion and hypersecretion associated with the common cold, sinusitis, vasomotor rhinitis and allergic rhinitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any component; concurrent MAO inhibitor therapy; severe hypertension; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Do not use 'Tuss-Ornade' Liquid in children less than six months of age or under 15 lbs. in weight. Do not use 'Tuss-Ornade' *Spansule* capsules in children under 12 years of age.

Warnings: Warn vehicle or machine operators of possible drowsiness. Warn patients of possible additive effects of alcohol and other C.N.S. depressants.

Usage in Pregnancy: Use in pregnancy, nursing mothers and women who might bear children only when potential benefits have been weighed against possible hazards. An inhibitory effect on lactation may occur.

Effect on PBI Determination and I^{131} Uptake: The iodine in isopropamide iodide may alter PBI test results and will suppress I^{131} uptake; use thyroid tests unaffected by exogenous iodides.

Precautions: Use with caution in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism. 'Tuss-Ornade' Liquid contains FD&C Yellow #5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow #5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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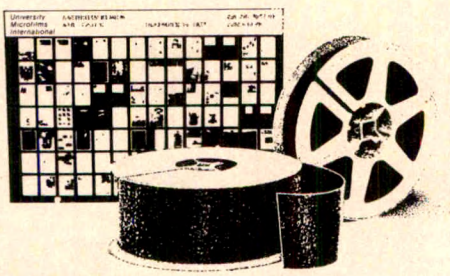

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Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Ilosone promptly.

Ilosone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

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When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient's strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least ten days.

Alpha-Hemolytic Streptococci (Viridans Group) – Short-term prophylaxis against bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin. (Erythromycin is not suitable prior to genitourinary surgery when the organisms likely to lead to bacteremia are gram-negative bacilli or belong to the enterococcus group of streptococci.)

Staphylococcus aureus – Acute infections of skin and soft tissue which are mild to moderately severe. Resistance may develop during treatment.

S. (Diplococcus) pneumoniae – Infections of the upper respiratory tract (e.g., otitis media, pharyngitis) and lower respiratory tract (e.g., pneumonia) of mild to moderate severity.

Mycoplasma pneumoniae (Eaton Agent, PPLO) – Respiratory tract infections due to this organism.

Haemophilus influenzae – May be used concomitantly with adequate doses of sulfonamides for upper respiratory tract infections of mild to moderate severity. Not all strains of this organism are susceptible at the erythromycin concentrations ordinarily achieved.

Treponema pallidum – As an alternate treatment in penicillin-allergic patients. In primary syphilis, spinal-fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae – As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

C. minutissimum – In the treatment of erythrasma.

Entamoeba histolytica – For intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes – Infections due to this organism.

Legionnaires' Disease – Although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Contraindication: Known hypersensitivity to this antibiotic.

Warnings: (*See* Warning box above.) The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy – Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering this antibiotic to patients with impaired hepatic function.

Recent studies of erythromycin reveal that its use in patients receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In such a case, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, overgrowth of nonsusceptible bacteria or fungi is possible. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported. [0130791]

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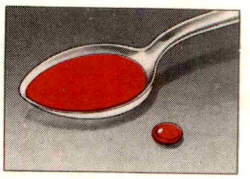

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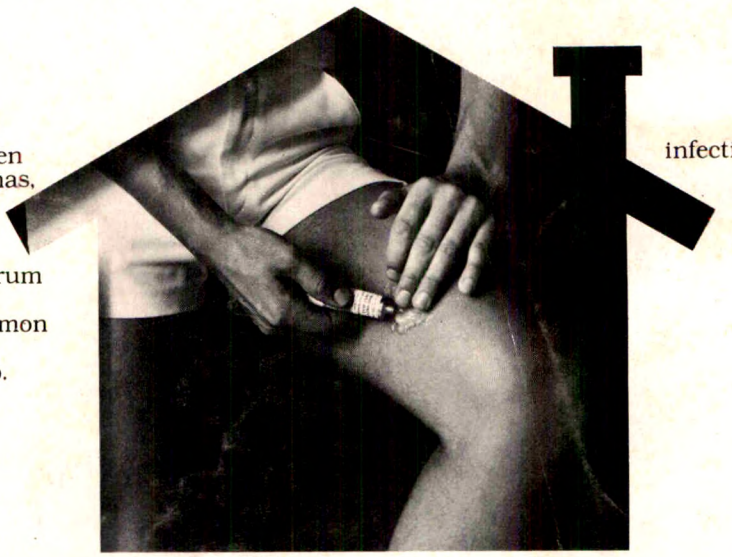

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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